Mitochondria pathogenesis and dysfunction in Alzheimer's disease

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Abstract

Mitochondria are well-known for their electrochemical nature and their ability to provide energy for the cell functions, characteristics which neurons depend on. Thus, any mitochondrial dysfunction may have a severe impact on neuronal functions and they can impel neurodegeneration as occurs in Alzheimer's disease (AD). High levels of Reactive Oxygen Species (ROS) and imbalance of Ca^{2+} homeostasis indicate neurodegeneration and they are observed in AD. Moreover, in neurons of AD patients, mitochondria differ in morphology, they are less at synapses and a catastrophe of the mitochondrial network occurs compared to healthy neurons. Oxidative stress is a characteristic of the early AD stages. In fact, it happens before the massive Amyloid protein (A_β) concentration and filament formation, and induces oxidative protein modifications, mutations on the mitochondrial DNA (mtDNA) and disorders on the mitochondrial membrane permeability. A_β peptide induces ROS formation and increases of Ca^{2+} concentration in mitochondria, which also boosts ROS concentration. Thus, formation of mitochondrial pores (mPTP) occurs, which release Ca^{2+} in the cytoplasm and, finally, neuron death is brought about. Furthermore, p53 protein is increased in AD neurons, which is probably associated with the high A_β concentration, and results in apoptosis. At the same outcome, leads the Tumor Necrosis Factor (TNF-a) secretion, as a result of FasL activation by A_β peptide. Consequently, mitochondria play a prominent role in neurodegeneration and their dysfunction seems to be the reason for AD development, as they differentiate abnormally before the first symptoms. Therefore, mitochondria can be a target for AD drug development.

Introduction

Alzheimer's Disease (AD) is a neurodegenerative disease, with a slow and progressive pace of degeneration, which causes the loss of cognition. A characteristic of AD is the accumulation of senile plaques in brain, which are made from the beta-amyloid (Aβ), which comes from the post-translational proteolysis of the Amyloid Precursor Protein (APP), a procedure that is strictly regulated by β- and γ-secretase [1]. However, the most severe characteristic is the neurofibrillary tangles (NFTs) formation, a result of intracellular accumulation of Tau protein. In this case, Tau self-polymerizes and aggregates in the NFTs. Moreover, a posttranslational modification of the same protein in the cell occurs. Tau Protein is a Microtubule Associated Protein (MAP), which normally keeps the microtubules in a body, in order to perform their in-cell roles. However, the phosphorylation of Tau protein, which is the aforementioned posttranslational modification, avoids the protein to interact with the microtubules. There are three enzymes that are thought to take part in Tau phosphorylation in mammalian brain: GSK-3β, cyclin-dependent kinase 5 (cdk5), cAMP-dependent protein kinase (PKA) and calcium/calmodulin-dependent kinase II (CaMK-II) [2-4]. These two molecular mechanisms, the senile plaques and the NFTs formation, are the reason for neuronal synaptic failure that results in progressive neuronal loss [5].

For neurodegeneration, mitochondria seem to play a prominent role. For neurons, mitochondria are the major energy factories, since these cells have limited glycolytic ability [6-8]. Their allocation is determined by the need of ATP for the cell functions in specific intracellular loci and that is why they are found more often at areas where synapses occur. Synapsis as a physiological phenomenon demands high amounts of ATP [6], which stems from the mitochondrial function with Ca^{2+} buffer [9]. This allocated "need for enery" in a neuron, urges the mitochondria to transport from a locus to another, where their energy contribution is essential. However, this is not the one and only reason for mitochondria transport; neurons are postmitotic cells, which are supposed to survive for the lifetime of an organism and, thus, mitochondrial trafficking is a way to get rid of aged or damaged mitochondria [9, 10]. This trafficking phenomenon relies on cytoskeletal elements, mainly microtubules, but also actin filaments, and associated molecular motors (dynein, KIF5, myosin) for trafficking and proteins (syntaphilin) for anchoring [9]. Malfunction of the mitochondrial transport is one of the main reasons for neurodegeneration [9, 11].

Aβ oligomers (AβOs) that reside in brain neurons of AD patients interact with the mitochondrial membrane and the mitochondrial proteins. This means that AβOs constitute a block for several mitochondrial functions, such as insertion of the nuclear-coded proteins of mitochondria, breakage of the electron transport chain and ROS increase [12, 13]. It is clear that such intracellular conditions lead sooner or later to severe mitochondrial damages and, finally, bring about the neuronal malfunction [13], increasing the possibilities for apoptosis [14]. However, the neuron struggles to be kept alive and takes advantage of the mitochondrial capacity for fusion and fission [13]. The proteins in charge for mitochondrial fission in mammals are dynamin-related protein (Drp1) and mitochondrial fission 1 (Fis1), whereas for mitochondrial fusion are optic atrophy protein 1 (Opa1), mitofusin 1 and 2 (Mfn1/2) [15]. In this way, two dysfunctional mitochondria or a combination of a dysfunctional and a functional one can fuse into a healthy and functional one. At the same outcome can lead a procedure called mitophagy, which is referred to the autophagy of dysfunctional mitochondria. That is how cells are trying to keep their mitochondria, their main source of energy, healthy and functional, a prerequisite for cell longevity [16, 17]. However in AD, neurons do not always win the battle of survival and they are heading progressively to apoptosis, due to the presence of AβOs [18].

On this review, we discuss the impact of oxidative stress on mitochondrial function, as well as other intracellular events that lead to neuronal apoptosis, under the scope of AD. Additionally, we review the mitochondrial morphology

neurons of AD patients. In the end, we suggest mitochondria-targeted drug development for AD and we give directions for future research.

Oxidative stress, p53 and neuronal cell death in AD

Oxidative stress occurs during the very early stages of AD, before the massive AβOs formation and induces the oxidative modification of proteins, mitochondrial DNA (mtDNA) mutations and severe problems for the mitochondrial permeability. Oxidative stress not only occurs in AD, but also in other neurodegenerative diseases [19, 20]. Amyloid beta binding alcohol dehydrogenase (ABAD) is the first mitochondrial protein found to bind to the Aβ peptide. Aβ-ABAD complex induces ROS production and they leave mitochondria for the neuronal cytoplasm [21]. The negative impact for the neuronal function is brought about not only because of higher ROS concentration, but also because of loss of mitochondrial capacity to remove ROS [22]. Simultaneously, reduced expression of Superoxide dismutase (SOD) is found in AD patients [23, 24]. SOD enzymes catalyze the dismutation of the superoxide radical (O_2^-), a form of ROS, into molecular oxygen (O_2) or hydrogen peroxide (H_2O_2) [25, 26]. In other words, SOD enzymes tone down the oxidative stress and less concentration of them may constitute a problem as well. However, H_2O_2 is also damaging for the living cells, but comparatively less and they are degraded by catalases [26].

It is found that Aβ peptide induces increase of Ca^{2+} concentration in cytoplasm [27]. As a result, mitochondria are overcharged with Ca^{2+} a phenomenon that increases ROS, which affect negatively mitochondria as far as their permeability is concerned [28]. Mitochondrial Permeability Transition Pores (mPTPs) are formed and Ca^{2+} is released into the cytoplasm, bringing about neuronal necrosis [28, 29, 30]. Cyclophilin D (CypD) levels are significantly high in brain areas affected by AD progression, whereas in unaffected brain areas CypD levels are normal [31]. CypD interacts with Aβ peptide forming complexes in mitochondria [32]. It is found that Aβ peptide reduces the boundaries of mPTP in isolated mitochondria. Increase of relocation of CypD in the inner mitochondrial membrane is observed in mitochondria of AD patients [33, 34]. Exclusion of mPTP by knock-out of CypD gene suppresses Aβ-mediated activation of the p38 mitogen-activated protein kinase signaling pathway, normalizes mitochondria that reside in the neuronal axon, betters synapsis and weakens synaptic loss [35].

In brains of AD patients, it is found that p53 expression is higher than normal in damaged neurons, which leads to induction of apoptosis in a p53 related pathway [36, 37]. It is also found in transgenic mice, that the increased p53 concentration is related to the cytoplasmic expression of Aβ peptide, which may urge the FasL expression in neurons [38]. In parallel, activation of the microglial cells induces the secretion of Tumor Necrosis Factor a (TNFa), activating the TNF receptor 1 (TNF-R1), which results in apoptosis [19, 39]. Additionally, Aβ peptide may act specifically into astrocytes, bringing about ROS formation and loss ΔΨm mitochondrial force, facts that lead to neuronal death, along with the oxidative stress that occurs in astrocytes [40, 41]. However, there are data that indicate that neuronal death may occur without caspase activation; Aβ peptide urges Apoptosis Inducing Factor (AIF) to relocate from mitochondria to the nucleus. It is also possible that AIF induces alternative apoptotic pathways of cell death during AD, hindering mitochondrial functions [42].

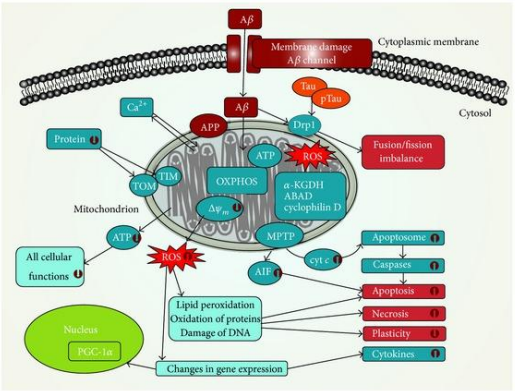

Figure 1. Mitochondrial dysfunctions in Alzheimer's disease. Amyloid-beta (Aβ) impairs the integrity of cytoplasmic membrane and causes mitochondrial dysfunctions. Aβ inhibits the activity of oxidative phosphorylation (OXPHOS) system, which can result in decrease of ATP production and increased reactive oxygen species (ROS) formation. Decreased ATP production leads to impairment of ATP-dependent processes, where all cellular functions are involved. Decrease of mitochondrial membrane potential ($\Delta\psi_m$) is followed by opening of mitochondrial permeability transition pores (MPTPs). Release of cytochrome c (cyt c) and other proapoptotic factors from the intermembrane space of mitochondria induces the formation of apoptosome and consequently triggers activation of caspases and apoptosis. Apoptosis inducing factor (AIF) is a proapoptotic factor released by mitochondria. Disengaged AIF is transported into nucleus and triggers caspases-independent apoptosis. Phosphorylated tau protein (pTau) and Aβ cause enhanced nitrosylation of dynamin-related protein-1 (Drp1) leading to impaired mitochondrial dynamics, increased mitochondrial fission, and neurodegeneration. Further, Aβ inhibits the import of proteins into mitochondria and reduces activity of mitochondrial amyloid-beta binding alcohol dehydrogenase (ABAD), α-ketoglutarate dehydrogenase complex (α-KGDH), and cyclophilin D. Ability of mitochondria to handle Ca2+ is impaired by Aβ and Aβ precursor protein (APP); consequently overload of mitochondrial calcium leads to decrease of Δψm, opening of MPTPs, releasing of proapoptotic factors, increased ROS production, and decreased ATP production. PGC-1–peroxisome proliferator-activated receptor-gamma coactivator-1-alpha; TIM–translocase of the inner membrane; TOM–translocase of the outer membrane. (Courtesy of Dr. Jana Hroudova - This figure along with the accompanied caption was originally published by Hroudova et al., 2014 [43])

Mitochondria damages and morphology in neurodegeneration

Mitochondrial dysfunction - including the massive accumulation of ROS, mitochondrial permeability problems, ΔΨm disruption, inadequate ATP production, mtDNA mutations, imbalance of Ca^{2+} homeostasis, apoptotic factors release, mitochondrial transport errors, imbalance between mitochondrial fission and fusion – causes synaptic dysfunction and progressively brings about neuronal death [6, 43]. Mitochondrial dysfunctions are characteristic pathological changes of neurodegenerative diseases (NDs). However, not all NDs are characterized by the same pathological modifications. mtDNA is the major target of ROS; in miscellaneous ND cases point mtDNA mutations are observed, as well as various modifications, broad DNA deficiencies and basic mtDNA replication rate [44, 45, 46, 47]. The fact that NDs are more

often in aged population, could be explained by the accumulation of mtDNA chain mutations as years pass by [48]. In AD cases there have been identified some specific mutations related to complexes of the respiratory [49]. However, studies indicate that such mtDNA mutations are not strictly specific for neurodegeneration, but they are related to damages of specific neurons as a response [50, 51, 52].

Opa1 and Mfn2 play a prominent role in mitochondrial morphology in neurons. In young neurons, Mfn2 expresses in a higher level and Drp1 in a lower level than normal, which indicates that regulation of mitochondrial morphology occurs time and space dependently (in neurons) [53, 54]. Induction of neurodegeneration may also be due to imbalance of mitochondrial fission and fusion [55]. Neurotoxins, oxidative stress and mutations in Mfn2 and Opa1 genes may alter the morphology of mitochondrial network and hinder the bioenergetics of mitochondrial function or mitochondrial transportation, facilitating neurodegeneration [56, 57, 58]. Mutations in Mfn2 may be responsible for imbalance of the Ca^{2+} homeostasis and as a result for the overcharge of cytoplasm and mitochondria with Ca^{2+} with a severe impact on mitochondrial morphology and cell survival or death, as presented on figure 2 [59].

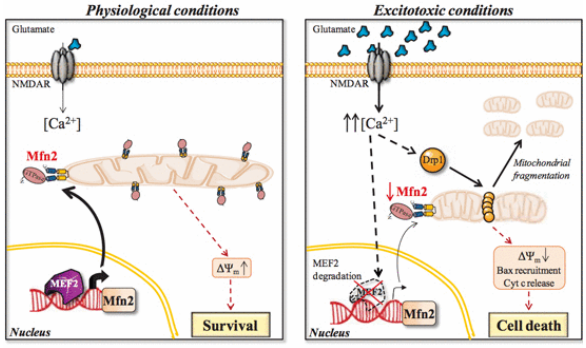

Figure 2. Excitotoxicity leads to mitochondrial fragmentation, altered calcium homeostasis and neuronal death in two phases: a reversible Drp1-dependent one, followed by the irreversible degradation of MEF2, causing reduced Mfn2 transcription and Bax translocation to mitochondria. (This figure along with the accompanied caption was originally published by Martorell-Riera et al., 2014 [59])

Drug development for AD – Mitochondria targeted drugs constitute a new era

It was initially conceived that the target for drug development for AD should be Aβ peptide [60, 61]. Therefore, clinical trials focused on eliminating the Aβ peptide from the brain of AD patients. A first conception supported that β- and γ-secretase enzymes should be inhibited, so as to hinder Aβ plaques formation [62, 63]. However, γ-secretase is important for Notch and other transmembrane proteins modifications [64, 65]. Even though the first results for this drug were promising, it was found that the drug concentration in the Central Neural System (CNS) was pretty low, which meant that Aβ peptide was probably the wrong drug target [66, 67, 68]. Another way for Aβ elimination was the immunotreatment with special antibodies for Aβ peptide [69, 70]. This way of treatment has given positive results for AD therapy, without activating the microglial cells and, as a result, causing inflammation [71, 72]. Such drugs are still under clinical trials.

The most up to date perceptions about ND treatment, including AD, set mitochondria as target, as summarized on figure 3 [73]. Major strategies for such drug development focus on ROS elimination, mitochondrial gene therapy and ways to inhibit the mPTP function [74, 75, 76, 77]. Relying on the fact that oxidative stress is the major factor for mitochondrial dysfunction, a thorough research has been carried out about the effectiveness of antioxidants as drugs for neurodegenerative diseases and, as a matter of fact, for AD [78, 79]. Reducing molecules, such as Vitamins C and E (VitC and VitE), glutathione and coenzyme Q10 (Co Q10) play a protective role for mitochondria against ROS. Low expression levels of such molecules are observed in various neurodegenerative disorders. VitC and VitE are crucial nutritional substances for the physiological functions in human. VitC is a powerful intracellular reducing molecule, whereas VitE contributes to removal of oxidized lipids in brain [80, 81, 82]. These two substances, consequently, can oxidative stress. However, Blood Brain Barrier (BBB) is a severe obstacle even for VitC and VitE. In this way protect the brain from, there has been developed a form of VitE, called MitoVit E, which is aims mitochondria specifically, which is able to accumulate in mitochondria due to an added lipophilic cationic substance called triphenyl-phosphonium. MitoVit E can enter mitochondria without disrupting ΔΨm and mitochondrial respiratory chain [83, 84, 85]. However, MitoVit E has yet to be applied to animal models and, thus, its therapeutic capacity is not known.

Coenzyme Q10 (Co Q10) mainly resides on the internal mitochondrial membrane and takes part in electron transport and removes ROS from mitochondria [86, 87]. In this way, Q10 prevents neurons from the oxidative stress induced cell death. ΔΨm is stabilized, CytC is not released in the cytoplasm and prevents mPTP formation [88, 89]. Thus, Co Q10 can work as a strong antioxidant drug for AD [89]. For the same reason as above, Mito Q, an analogue of Co Q10 was developed, which acts as a strong antioxidant that can remove ROS and can be recycled in the respiratory chain. Therefore, Mito Q can alleviate neurons from oxidative stress and prevent apoptosis, as it can improve mitochondrial dysfunctions [90, 91, 92, 93].

There are several antioxidant substances that stem from pharmaceutical plants and are able to protect mitochondrial function. For instance, green tea consists of polyphenols, which are considered to be strong antioxidants against ROS, nitrogen monoxide (NO) and oxidization of lipids [94, 95]. Green tea extracts, rich in polyphenols, are thought to reduce the Aβ peptide production in mice that overexpress APP, increasing the α-secretase activity [96, 97]. Other antioxidants are ginsenosides are steroid-like substances and they can remove ROS protecting mitochondria and neuronal functions [98, 99].

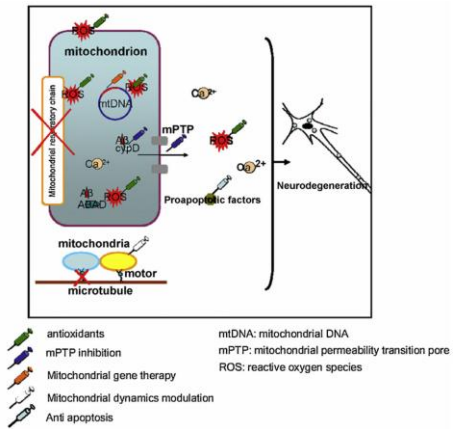

Figure 3. Schematic figure of therapeutic strategies to protect mitochondria against neurodegeneration. In neurodegenerative diseases such as AD, PD, HD and ALS, mitochondria undergo increased ROS production, suppressed respiratory function, mtDNA lesions, mPTP formation, preapoptotic factors release and damaged dynamics/motility. These deleterious factors will eventually lead to neurodegeneration. Mitochondrial medicine, including oxidant scavenge, mPTP inhibition, mitochondrial gene therapy, antiapoptosis and mitochondrial dynamics modulation, are promising therapeutic strategies to attenuate neurodegeneration and to halt the progression of neuronal injury in the neurodegenerative diseases. (This figure along with the accompanied caption was originally published by Du et al., 2010 [73])

Conclusions

To recapitulate, mitochondria seem to play a multidimensional role in NDs. Oxidative stress constitutes a scourge for the neuronal functions of brain and mitochondria give the first responses to this stress; they either strive for cell survival or, if the damages are irreversible, they give the signal for cell death. The borderline between these two options is not vague whatsoever; mitochondria are the main source of energy for neurons and any undesirable change in their function will lead to cell death. The aforementioned ROS and Ca^{2+} homeostasis are the first signals for cell death or survival. If the neurons are able to remove ROS and alleviate them from the oxidative stress, then Ca^{2+} concentration is kept in a balance and finally cells survive. To the contrary, if they are unable to remove ROS, high Ca^{2+} concentration is capable of bringing about neuronal death, after a cascade of molecular reactions. An additional unique feature of mitochondria, which is to undergo fission and fusion, provides the ability to create healthy mitochondria, in case of occurring cell stress, or to recycle its contents normally.

Oxidative stress and mitochondrial responses seem to be the reason for AD and not the outcome, as it was initially conceived. Therefore, up to date drug development targets mitochondria, examining the effect of various antioxidants. However, a greater investment in mitochondria targeted drug development should be made; the “hot” targets for AD drugs are eradication of ROS, attenuation of mPTP functions or apoptotic factors and balanced mitochondrial respiratory chain function. Research results for such targets indicate improvement of AD and, simultaneously, they are a promise for AD drug research. Antioxidants may assist the function of such drugs, by helping with the ROS eradication.

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Social cognition in adults: the role of cognitive control

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Abstract

Aim: This study aimed at examining the direct and indirect, via cognitive control and emotion recognition, effects of advancing age on adults' social cognition, and especially, on complex forms of it such as indirect speech, faux pas, and social mental verb understanding. **Method:** The sample comprised a total of 70 adults, aged from 18 to 83 years. Participants were almost equally distributed in each one of three age-groups (young, middle-aged, and older adults), according to their gender and educational level. Three tasks measuring the ability to interpret indirect speech, the ability to understand faux pas, and social mental verb understanding, respectively, were administered as measures of social cognition. Cognitive control, as inhibitory control, task switching, updating-monitoring, and planning, as well as basic emotion decoding from visual cues, were measured by four and one task respectively. **Results:** After the confirmation of the factor structure of each one of the dimensions of social cognition, and the examination of the direct effects of age on them, the all-inclusive path model finally confirmed showed that age has a significant negative indirect effect, via cognitive control, on social cognition as ability to interpret indirect speech and faux pas. **Conclusion:** The decreased performance that cognitively healthy older adults exhibit, as regards specific complex dimensions of social cognition, could be attributed to negative effects of age on cognitive control. However, it is likely that some other complex dimensions of social cognition are not affected by frontal aging.

Introduction

Social cognition includes automatic and voluntary cognitive processes applied for decoding and encoding the social world [1]. It is defined as the ability to represent mentally the relations between ourselves and other people, as well as the use of these representations to guide social behavior [2]. In fact, social cognition is a higher-order cognitive process that serves interactions [3] and leads to coherent interpersonal relationships [4]. As such a complex process, it comprises a set of abilities. Theory of Mind (ToM), namely the ability to attribute the full range of mental states, is the most representative and most studied dimension of social cognition [5]. At the theoretical level, a distinction is made between two broad dimensions of ToM: a. the cognitive dimension that refers to the ability to make inferences about cognitive states, such as beliefs, thoughts, and intentions [6]; b. the affective dimension that represents the ability to infer the feelings, affective states and emotions of others [7]. Recent studies in the field of social and cognitive neuroscience have identified a number of specific components of ToM.

A core component is called 'first-order' ToM and concerns the ability to draw conclusions about a person's mental states, like beliefs and thoughts (e.g., I think that Mr. X thinks that...) [8]. 'Second-order' ToM, a more complex form of ToM [9], corresponds to more internal representations about ourselves, and involves the ability of simultaneously adopting two perspectives (e.g., Mr. X thinks that Miss Y thinks that…) [10]. Higher metarepresentations are involved in more advanced ToM components, such as the comprehension of 'indirect speech' and 'faux pas'.

Indirect speech is ubiquitous in 'everyday' social interactions, when people make jokes or speak ironically or sarcastically [11]. The indirect meaning arises from the fact that there is a discrepancy between the literal meaning of the words and the social context [12]. In order to understand indirect speech, someone should comprehend speaker's intentions and other mental states, such as beliefs and feelings [13]. Specifically, understanding indirect speech requires first-order ToM as regards the speaker's belief, to avoid interpreting it as a mistake, as well as second-order ToM as regards the speaker's belief about the listener's belief, to avoid interpreting it as a lie [14].

Faux pas is a particular case of a non-intentional action. A faux pas occurs when a speaker says something without considering if it is something that the listener might not want to hear or know, and which typically has a negative outcome on the listener that the speaker never intended. It implies both the ability to refer to other's state of mind and the appreciation of the emotional impact of their statement on their listener [15]. Faux pas involves both cognitive and affective ToM, as faux pas understanding requires the ability to infer epistemological mental states, intentions and emotions. Specifically, in order for a faux pas to be identified, one should understand that the speaker did not realize that the statement should not have been said and that the listener may feel sad or upset [16]. The understanding that the speaker's intention was not malicious is also required [13].

Mental verbs are claimed to contribute to ToM [17]. From the semantic point of view, mental verbs relate to the 'language of mind' [18] and assist the understanding of our own and other's mental states. Philosophers of language distinguish some subclasses within the general class of mental verbs, like cognitive mental verbs (know, remember, understand etc.) and social mental verbs (promise, agree, suggest, etc.), with cognitive mental verbs denoting a true event (factive) described in the complement clause, and social mental verbs denoting an obligation or intention, stating reasons, arguments and communications [19]. Hence, by definition, it is obvious that social mental verbs are very strongly interconnected with social cognition and ToM. In any case, in order to judge a mental verb about the factivity or nonfactivity, it is necessary one to be able to separate mind content (mental representation) from reality [20].

Moreover, emotion recognition, which is an important but somehow instinctive and primitive social skill, is suggested to be interlinked with social cognition and empathy [21]. In particular, the ability to decode emotions from facial expressions seems to be related with the affective ToM, as it was found that the brain areas which are activated during these functions are overlapped [5]. In addition, in a recent study where older participants performed lower that younger ones, in faux pas discrimination, it was found that emotion recognition fully mediated age effects, [22]. These results provide evidence for the role of emotion recognition in a range of important social deficits.

As regards the pattern of social cognition's changes with age, there is still no clear research conclusion. This is true in particular for ToM, as the number of empirical studies is limited, and although most of them have concluded that there is a decline, there are contradictory findings in the literature. The first study aiming to investigate ToM in aging [23] found that older adults were more efficient than younger ones, in terms of their performance on the 'Strange Stories test'. This is a ToM task in which participants have to make inferences about what one character thinks about the mental state of another character, by decoding sarcasm, irony or social rule violation. Conversely, in a recent study, it is reported that young-old and old-old adults performed more poorly than young participants on a similar task, except when cognitive load was reduced. These findings show that older adults are impaired only on ToM tasks with high cognitive processing demands [24]. In the same vein, age-related declines in ToM were found, when second-order ToM tasks requiring participants to consider the thoughts of two different characters, were used, while less complex first-order ToM was not impaired with age. This could indicate that, rather than showing a specific deficit in the ability to represent mental states, older adults show a decline in the domain-general resources required for complex ToM judgments [25]. However, such a conclusion is also debatable, as preservation of more complex forms of ToM, like faux pas, has been supported by other studies [26].These discrepancies may have arisen from methodological limitations, such as ceiling effects, small samples or the use of tasks with different demands for assessing the same ToM component. In particular, the older studies tended to examine a single ToM component or use only one type of task to measure it [10]. Nevertheless, recent research suggests that different dimensions of social cognition and ToM follow different developmental trajectories [27].

Regardless of the uncertainty about the identification of social cognition's dimensions that appear to be impaired in normal aging, another important issue concerns the relation between these impairments and deterioration of other cognitive functions. Aging is known to be accompanied by irreversible changes at a cellular level that evolve progressively with age [28]. As regards central nervous system during normal aging, many changes occur in brain's structure and function [29]. As a result, cognitive functions seem to be affected to a greater or lesser extent [30]. Neuropsychological research demonstrates a cognitive profile of contrasts in aging, as some main functions display deficits, while others remain intact [31]. Impairments in functions that are supported by frontal lobe, such as cognitive control or as it is usually called, 'executive functions', are well documented [32]. It has been suggested that executive functions are strongly required during the production of a social inference, and therefore, are involved in ToM, throughout lifespan development [33]. Thus, it is interesting to examine their contribution in ToM performance in aging. Previous studies showed conflicting results. Some of them concluded that the deterioration in cognitive ToM components observed in healthy older adults is a result of an age-related decline in executive functions, like inhibitory control, rather than an impairment of the actual system for representing mental states {34-35}. However, at least one recent study clearly shows that age-related decline in ToM is not attributable to age-related impairment in executive functions [24].

Based on the theoretical framework, it seems that despite the fact that, recently, research interest has shifted to the investigation of social cognition in aging, clear conclusions about which are the dimensions of social cognition that are affected by age, as well as about the role of other cognitive functions in the developmental trajectory of ToM have not been formulated. In this light, the present study was designed to examine adults' ability to understand higher-order dimensions of social cognition and ToM, which are less studied formerly, and explore the effects of age, gender and education on these abilities. The study aimed also at examining the relations among social cognition, emotion recognition, cognitive control, and individual - demographic factors.

The *hypotheses* of the study were formulated as follows:

1. Although deficits in less complex dimensions of social cognition in older adults than the abilities selected to be examined in this study have been confirmed by previous research, the effects of executive functions on social cognition decrements seem to be decisive. Therefore, it was assumed that age would not have any direct effect on any one of the dimensions of social cognition that the present study aimed to examine.

2a. According to several studies, impairments in social cognition with age are mediated by executive functions, which are also impaired. Thus, it was suggested that there would be an indirect negative effect of age on social cognition, through cognitive control.

2b. Apart from the hypothesized indirect effect of age on social cognition via cognitive control, this study aimed also at examining potential effects exerted by age on social cognition, via the ability of emotion recognition. Data in this field are limited. Only one study found that age affect indirectly and negatively, via emotion recognition, the ability to understand faux pas [22]. Hence, it was assumed that there would be indirect negative effects of age on the dimensions of social cognition involving affective elements, like understanding of faux pas where empathy is required, and understanding of indirect speech, which requires, among others, inferring the feelings of the speaker.

3. The effects of individual - demographic factors, like gender and educational level, on adults' social cognition have attracted little research interest. For this reason, a specific aim of the present study was to examine their direct effects on social cognition's dimensions. According to one study [36], older adults' impaired performance on social cognition was not affected by educational level. Hence, it was assumed that there would not be direct effects of this factor on social cognition's dimension.

Method

Participants

The sample comprised a total of 70 adults (34 women) from Greece, who participated voluntarily in the study. As regards the age of the participants, the sample consisted of three age-groups: young, middle-aged, and older adults. Participants belonged to three different educational levels (EL): middle EL (n=25, 10 - 12 years of education), upper EL (n=19, ≥13 years of education - vocational/technical school), and high EL (n=26, ≥13 years of education - university and technological educational institute). Participants in each one of the three age-groups were almost equally distributed in terms of their gender, F (2, 67) = .046, p > .05, and educational level, F (2, 67) = .076, p > .05, with no statistically significant differences between the age-groups (Table 1). The sample of the 70 participants was the final one, after the exclusion of persons who met the exclusionary criteria used in the study. Exclusionary criteria for all possible participants were the presence of uncorrected hearing or visual loss, and a history of mental illness (depression symptoms and/or a history of psychosis) or substance abuse. The presence of depressive symptoms in the older adult group was examined with the Geriatric Depression Scale-15 (GDS-15). Taking into account the financial crisis in Greece, a relatively flexible criterion for exclusion (a score more than 8) of the older adult participants on the basis of their GDS-15 score was adopted, considering that the GDS-15 score '6-7' was confirmed as a valid cutoff level for the diagnosis of older adult depression in Greece [37]. To investigate the existence of depressive symptomatology in young and middle-aged adults, the Beck Depression Inventory (BDI) was administered. Potential participants who scored over '30' were excluded, as this rating is an indication of serious clinical depression [38]. Additional exclusionary criterion for the older adult participants was the existence of cognitive decline. A score lower than '23-24' in the Mini Mental State Examination (MMSE) is considered indicative of cognitive impairment [39]. However, in this study, to ensure that older participants were cognitively healthy, a more stringent criterion was used, as a score lower than 27 excluded the potential participant.

Measures

Social cognition

Indirect Speech Understanding Task: Irony, Humor, Sarcasm (ISUT). Based on ''Strange Stories test" [23], the ISUT was developed by Natsopoulos, for the purposes of the present study, as a part of a battery of tasks aiming at examining different complex dimensions of social cognition. The ISUT contains nine stories (three of each form of indirect speech, namely of irony, humor, and sarcasm), in which the protagonists say something that are not meant literally. Every story is read by the examiner. Initially, the participant is asked to answer a series of control questions, in order to examine whether they cognitively understand the story. This is a prerequisite to proceed with the following step. Then, the participant's task is to answer the main two questions developed to examine ToM. In the first, the participant has to answer if the protagonist's statement is true. Only if the answer to this question is ''no'', suggesting that the non-literal meaning of the story is understood, the second question, that is ''Why did he/she say that?'', is given. In order for the interpretation of the indirect speech to be considered "correct", it is necessary the participant to understand the motivations and various mental states of the person who expresses something not literally. As regards scoring for the ISUT, every correct answer, for the main two questions, is credited with '1' and every incorrect answer is taking '0'. An example item of the task is the following: Philip is reliable worker. His employer cuts a significant amount of his fixed fee. Philip disappointed says: "I did not expect such a consistency! I am very willing to work with you in the future!''

Table 1. Participants' distribution according to age, gender, and educational level

Adult participants Age-group	Age Range	(years) Mean	*SD*	Gender Male	Female	Middle	Education Upper	(years) High	GDS* Mean (*SD*)	MMSE** Mean (*SD*)	BDI*** Mean *(SD)*
Young (n=26)	18-30	23.4	*4.0*	14	10	10	5	11			
Middle-aged (n=20)	35-58	45.8	*6.7*	10	10	7	7	6			4.8 *(5.9)*
Older (n=24)	65-83	71.6	*5.8*	12	12	8	7	9	1.4 (*1.4*)	28.8 (*1.6*)	4.0 *(4.2)*
Total sample (N=70)	18-83	47.1	*21.2*	36	34	25	19	26			

*GDS = Geriatric Depression Scale; **MMSE = Mini Mental State Examination; ***BDI= Beck Depression Inventory

Faux Pas Understanding Task (FPUT). This task, consisting of three stories, was developed on the basis of a test described in Stone, Baron-Cohen, and Knight (1998) [40].The stories contain scenarios that tell about a faux pas. After the reading of each story by the experimenter, the participant is asked six questions about important details of the story, as a control for story comprehension. This step is a prerequisite to proceed with the next questions related to ToM. Then, the participant is asked a faux pas detection question: "Did anyone say something that it shouldn't have been said? Did anyone say something awkward?" If the participant answers ''yes'', they are asked "Who said something that it should not have been said?" Then three more demanding -in terms of ToM- questions are asked: "Why shouldn't the individual in the story have said what they did?" This question examines whether the participant is able to understand that the listener would be hurt or insulted. In fact, this is an inference about affective mental states. The next question is "Why do you think they did say it?" This question examines whether the participant is able to understand that the faux pas was unintentional. This is an inference about epistemic mental states and intentionality. The final question is "How do you believe that the person who listened something that it shouldn't have been said, felt?" Again, an inference about affective mental states is needed. Each correct answer, only for the questions related to ToM, scores "1" point. Every incorrect answer is taking '0'. An example item of the task is the following: Fotini rents new apartment and buys new curtains... Her friend, Elpida, visits her to see the apartment. She says "curtains are crap! I hope to buy soon new!"

Social Mental Verb Understanding Task (SMVUT). To examine adults' ability to understand the social factor together with the indeterminate (nonfactive) 'nature' of social mental verbs, the SMVUT was used [41]. The SMVUT includes three social mental verbs (promise, propose, agree), each one from which is contained in four, very short, main clauses, and is given half the time in affirmative and half the time in negative form. This task examines the ability to make inferences from social nonfactive mental verbs. As regards scoring for the SMVUT, every correct answer is credited with '1' and every incorrect answer is taking '0'. In order to compare adults' performance as regards social mental verb understanding with the respective performance regarding cognitive (factive) mental verb understanding, a cognitive mental verb understanding task was also administered [41]. This task was designed to examine a person's ability to draw inferences from factive mental verbs. It includes three cognitive mental verbs (know, remember, forget), which are contained in four, very short, main clauses, and are given half the time in affirmative and half the time in negative form. An example item of the task is the following:
Anthimos proposed to Pericles to play basketball with the school team.
Who is going to play basketball: A. Pericles? B. Anthimos? C. I can't decide''.

Emotion recognition
The 'TASIT- PART I: Emotion Evaluation Test (EET – PART 1 – FORM A) [42]. The EET was designed to examine a person's ability to identify six basic emotions, namely happiness, pleasant surprise, sadness, anger, anxiety, and disgust, and discriminate these from neutral expressions, when they are portrayed dynamically by professional actors. Specifically, it comprises 28 alternative forms of a series of short (15-60 seconds) videotaped vignettes of people interacting in everyday situations. After viewing each scene, the participant is asked to choose the emotion displayed by the actor from a list of six emotional categories and one non-emotional category (neutral) displayed in random order on one of five Response Cards. All scripts are neutral in content and do not lend themselves to any specific emotion. However, considering that the test was developed in English, for the purposes of the present study, we decided to administer it with the sound turned off, so as to focus on the person's ability to read dynamic visual cues. As regards scoring, a total score for correct decoding of each one of the six emotions and the neutral condition is calculated. Thus, the score for every emotion and the neutral condition could range from '0' to '4'.

Cognitive Control
Delis - Kaplan Executive Function System (D-KEFS) [43]. This battery provides a standardized assessment of higher-order cognitive functions supported by the frontal lobe (executive functions). It is composed of nine stand-alone tests. In the current study, the following tests were administered: a) the Verbal Fluency Test which assesses main executive functions (inhibitory control, task switching), long term memory, verbal intelligence, attention, reaction time and the ability to use strategies; b) the Design Fluency Test which assesses the same executive functions (inhibitory control, task switching) plus cognitive flexibility, nonverbal creativity, the ability to create optical patterns, as well as simultaneous processing of stimuli; c) the Tower Test which assesses forward planning of a sequence of steps, as the participant tries to move a pattern of discs efficiently from a start configuration to a goal configuration to match a target pattern, the ability to apply specific rules, inhibitory control, rule switching, and updating-monitoring. As regards scoring, in Verbal and Design Fluency Test, a total score for the correct answers for the three conditions that composed each one of the tests, is calculated. In Tower Test, the total achievement score is based on how many towers were correctly completed in the allotted time and how many moves were required to complete them.
Example items:
In one condition of the Verbal Fluency Test is requested the following; ''Say as many animals as you can in one minute''.
In one condition of the Design Fluency Test is requested the following; ''Draw as many patters as you can in one minute, by linking the black dots with four lines".

Working memory task: Short-Term Retention and Processing Task: Central Executive (STRPT: CE). The task involves listening recall and it was designed based on the working memory battery of Pickering and Gathercole (2001), to test the functions of the central executive. This task is a dual-processing task and is administered in order to assess storage capacity and dual processing [44]. Participants are asked to listen to a sentence, then state whether its content is true or false. After doing so for all sentences in the set, they have to repeat the last word of all sentences in the set. Each memory span includes six trials, and if they answer four correctly, they advance to the next span level. If they answer three or fewer out of six trials incorrectly, the test must be discontinued. The variable of interest is the largest memory span achieved, which is calculated by the range of the previous span level where the test was disconnected. The memory span could be ranged from '2' – '9'.

Statistical Analyses
Confirmatory factor analysis (CFA), the technical construction of multiple indicators equations - multiple causes (Multiple Indicators Multiple Causes Modelling - MIMIC), and path analysis (Path Modelling) that will be presented below were conducted in EQS Version 6.1. [45]. Because of kurtosis, all the aforementioned SEM techniques were performed on covariance matrices using Robust Maximum Likelihood estimation procedure. Model fit was evaluated based on the Satorra-Bentler scaled chi-square statistic as well as on the root mean squared error of approximation (RMSEA); a rule of thumb is that RMSEA $\leq$ .05 indicates close approximate fit, and RMSEA $\leq$ .06 indicates good fit. The Comparative Fit Index (CFI) was also used; CFI values greater than .90 indicate reasonably good fit of the model [46].

Procedure
The examination process began with the completion of the individual – demographics information. Thereafter, the tests which ensured that the participants met the inclusion criteria were administered. During the first session of the examination, the tests of social cognition were administered in random order, and during the second session, the tasks of cognitive control

and emotion recognition wee administered in random sequence. Before the examination, participants gave written informed consent for their participation in the research.

Results

Structural validity of the Indirect Speech Understanding Task (ISUT): Irony, Humor, Sarcasm

In order to examine whether there are any underlying, broad dimensions based on which indirect speech understanding is achieved, the data were subjected to confirmatory factor analyses (CFAs). Two alternative CFA models for the structure of the ISUT were examined. According to the existing literature, we firstly tested a two-factor model of the ISUT. Three observed variables, which were obtained from the answers to the first question in each form of story (namely the question examining the ability to understand the non-literal meaning of the speech), were set to load on a factor labelled 'First-order Theory of Mind'. Three observed variables, which were obtained from the answers to the second question in each type of story (namely the question examining the interpretation of the indirect speech and requiring the discrimination of the correct form –irony, humor, sarcasm- of the indirect speech), were set to load on a factor labelled 'Second-order Theory of Mind' (measurement model 'A'). This model was not confirmed, showing that the two factors as they were defined represented a model that did not fit the data. The next CFA model tested was a single factor model in which all observed variables were set to load on a factor labeled 'Understanding of Indirect Speech' (measurement model 'B'). The model yielded an excellent fit. The chi-square goodness of fit test was not statistically significant, resulting in the acceptance of the null hypothesis of good fit, Satorra-Bentler scaled χ^2 (1, N = 70) = .16, p = .90. The CFI was 1.00, indicating strongly reasonable fit, and the RMSEA was .00 (90% CI: .00 - .19), indicating close approximate fit for the structural model 'B' (see Figure 1). However, it is important to mention that the variables found to load on the factor concerned only three of the nine stories, in particular one from each form of indirect speech examined (irony, humor, sarcasm). As regards internal consistency of the latent variable of the model, this was found to be low, as Cronbach's alpha was .54 for the 'Understanding of Indirect Speech' factor.

Indirect Speech Understanding Task performance

To find out the extent to which adults can distinguish the indirect speech from a sincere exchange, but also their ability to understand the intention for irony, humor and sarcasm, frequency analysis was performed. The best possible score was '6', given that only the scores from the answers to the questions of the stories that load on the factor 'Understanding of Indirect Speech' were considered as valid ones. The results showed that there is not any person credited with the best possible score. The best performance which was observed was '5' and only 20% of the participants (n=14) were credited with it. To identify whether the participants' greater difficulty was in the ability to distinguish indirect speech from a sincere exchange, or in the understanding of speaker's intention, analysis of frequency was performed separately for each of the two questions of the stories, and separately for the three forms of indirect speech. Regarding irony, 90% of the participants (n=63) responded correctly to the first question and understood that what was said was false. However, only 12.9% of the same participants (n=9) answered correctly to the second question and understood that what was said was ironic. In regards to sarcasm, participants understood that what was said was not true in a percentage of 91.4% (n=64), but only 11.4% (n=8) understood correctly speaker's intent for sarcasm. In fact, 47.1% of the participants (n=33) appeared to misunderstand sarcasm as irony. Similar difficulties were not found regarding humor, as the 91.4% of the participants (n=64) answered correctly the first question and 62.9% of them (n=44) understood correctly the speaker's intention.

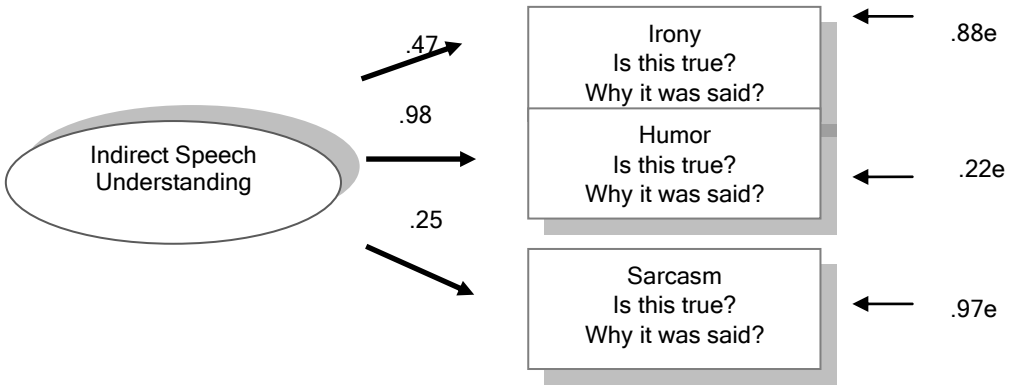

Figure 1. The underlying structure of the Understanding of Indirect Speech latent factor (standardized solution).
*All loadings drawn indicate significant associations (p < 0.05). **e = measurement error

Structural validity of the Faux Pas Understanding Task (FPUT)

Although similar tests have been used in several studies previously, there is no evidence for the factorial structure of such a test. Based on what is theoretically examined via the questions that constitute the FPUT, we firstly tested a single factor model of the FPUT. Six variables, which were resulted from the summative scores of the answers to the ToM-related questions of the three stories of the FPUT, were set to load on a factor labeled 'Faux Pas Understanding' (measurement model A). This model was not confirmed, showing that the latent factor as it was defined was responsible for the misspecification of the model. Inspection of the standardized solution revealed that the variable-indicator 'Did anyone say something that it shouldn't have been said?' (Faux pas identification question) had a non-significant loading

on the factor. Therefore, we tested a single factor model, where five of the ToM-related questions of the FPUT set to load on a latent factor labeled 'Understanding the commit conditions of Faux Pas', while the observed variable 'Identification of Faux Pas' was set to be free (measurement model B). The Wald and the Lagrange tests, which represent frequently used statistics to identify focal areas of misfit in a CFA solution, showed that three of the five variables had to be kept to load on the latent factor. Moreover, the latent factor and the free observed variable in the model should be allowed to correlate with each other. The modified model yielded an excellent fit. The chi-square goodness of fit test was not statistically significant, resulting in the acceptance of the null hypothesis of good fit, Satorra-Bentler scaled χ^2 (2, N = 70) = 1.13, p = .57. The CFI was 1.00, indicating strongly reasonable fit, and the RMSEA was .00 (90% CI: .00 - .20), indicating close approximate fit for the modified model (see Figure 2). At this point, it is important to mention that the three variables kept corresponded to the answers to the questions: 'Why shouldn't the individual in the story have said what he/she did?', 'Why do you think he/she did say it?', 'How do you believe the person that listened something shouldn't have been said, felt?' (see Figure 2). The internal consistency of the latent variable was found to be good, as Cronbach's alpha was .78 for the 'Understanding the commit conditions of Faux Pas' construct.

Faux Pas Understanding Task performance

In order to examine adults' performance in this task, analysis of frequency was performed. The results showed that participants had a well-formulated ability both to identify the Faux Pas and to understand the commit conditions of Faux Pas. The best possible score as regards the ability to identify Faux Pas was 'three points' and 81.4% of the participants (n=57) were credited with this. Regarding the ability to understand the commit conditions of Faux Pas, 21.4% of the total sample (n=15) responded correctly in the three questions for each one of the three stories (score = '9'), while the same proportion answered correctly in eight and seven questions (score = '8' or '7'). Looking in more detail the performance, participants appeared to have in a greater extent the ability to identify correctly the feelings of the person that listened something shouldn't have been said, as 71.4% of the participants (n=50) responded correctly in the respective questions.

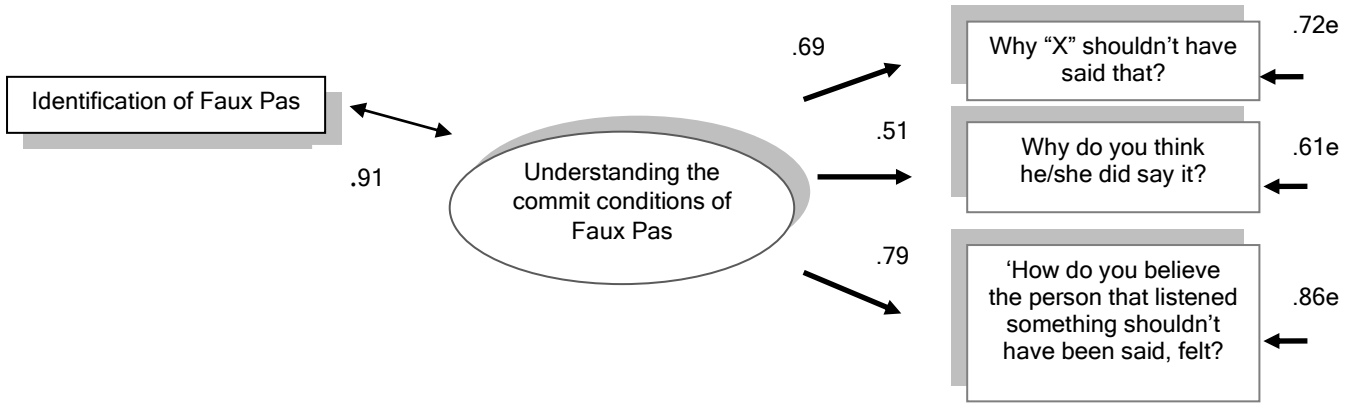

Figure 2. The structural model of the Faux Pas Understanding Task (standardized solution).
*All loadings and correlations drawn indicate significant associations (p < 0.05). **e = measurement error

Structural validity of the Social Mental Verb Understanding Task (SMVUT)

According to the extant literature, it is supported that the processing of affirmative and negative sentences differs, as each of them is mediated by distinct brain regions [47]. For this reason, we tested a two-factor model of the SMVUT. Three observed variables referring to social verb understanding, when the verbs are given in affirmative form, were set to load on a factor labelled 'Understanding of Social Verbs in Affirmative Form'. The remaining three variables referring respectively to understanding of each one of the same social verbs, when the verbs are given in negative form, were set to load on a second factor labeled 'Understanding of Social Verbs in Negative Form' (measurement model 'A'). The Lagrange test showed that the two factors in the model should be allowed to correlate with each other (structural model 'A'). This structural model yielded an excellent fit. The chi-square goodness of fit test was not statistically significant, resulting in the acceptance of the null hypothesis of good fit, Satorra-Bentler scaled χ^2 (7, N = 70) = 5.64, p = .58. The CFI was 1.00, indicating strongly reasonable fit, and the RMSEA was .00 (90% CI: .00 - .13), indicating close approximate fit for the structural model 'A' (see Figure 3). As regards internal consistency of the two latent variables, Cronbach's alpha was .70 and .78 for the 'Understanding of Social Verbs in Affirmative Form' and the 'Understanding of Social Verbs in Negative Form' factor respectively.

Social Mental Verb Understanding Task performance

The results from the analysis of frequency showed that adults did not possess a well-formulated level of social mental verb understanding. There was not any person credited with the best possible score as regards the ability to draw inferences from social - nonfactive verbs given in affirmative form, while only 7.1% of the participants (n=5) were credited with the best score for their ability to draw inferences from social - nonfactive verbs given in negative form. In fact, 51.4% (n=36) and 37.1% (n=26) of the participants were found to mistakenly attribute the meaning of all three verbs in affirmative and negative sentences, respectively. In sharp contrast, adults were found to posses the ability to draw inferences from cognitive - factive mental verbs, as 77.1% (n=54) and 42.9% (n=30) of the participants were credited with the best score, when the cognitive mental verbs were given in affirmative sentences and in the negative form respectively.

Direct effects of age, gender and educational level on understanding of indirect speech, faux pas, and social mental verbs
To examine the effects of age, education, and gender on the ISUT, FPUT and SMVUT, the Multiple Indicators Multiple Causes (MIMIC) modelling technique was used. In MIMIC models, both the latent factor and its indicators are regressed onto exogenous variables added to a CFA model established previously. MIMIC models were not confirmed, a finding that indicates that there was not any effect of age and the other two individual-demographic factors on the ability to understand indirect speech, on faux pas understanding, as well as on the ability to understand the indeterminate 'nature' of social mental verbs.

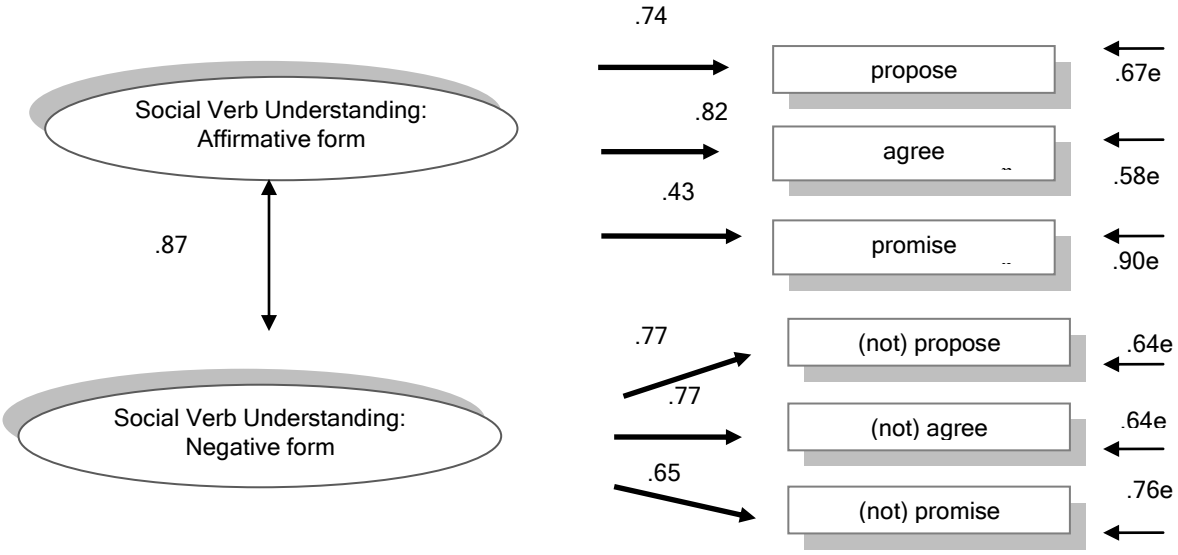

Figure 3. The structural model of the Social Mental Verb Understanding Task (standardized solution).
*All loadings and correlations drawn indicate significant associations (p < 0.05). **e = measurement error

Directed relations of age, gender, cognitive control, emotion recognition, and social cognition
In order to examine the directed relationships between age, gender, cognitive control, emotion recognition, and social cognition, all the latent variables were transformed to new observed variables. Cognitive control, as resulted from the respective CFA, was loaded by the following variables - indicators: design fluency (.45), planning-tower test (.56), working memory (.51), semantic fluency (.89), semantic fluency, after rule switching (.80), and rule switching score (.84). Basic emotion decoding was loaded from the variables - indicators: happiness decoding (.39), pleasant surprise decoding (.50), sadness decoding (.42), anxiety decoding (.52), and disgust decoding (.55). In the same CFA model, neutral expression decoding and anger decoding represented observed variables allowed free.

Each one of the newly created variables represented the summative score for the answers to questions - indicators that were found to load on the respective latent variable. After that, all relevant variables were subjected to recursive path analysis. The all-inclusive path model finally confirmed (path model 1), Satorra-Bentler χ^2 (68, N =70) = 74.70, p = .27, CFI = .96, RMSEA = .04 (90 % CI: .00 - .08), showed that age affected directly, negatively, and moderately emotion recognition, and indirectly, negatively, and moderately, through cognitive control, the recognition of emotionally neutral expression (Figure 4).

With regard to complex social cognition, age was found to affect indirectly, negatively, and moderately, and only via cognitive control, the 'Understanding of Indirect Speech', the 'Understanding the commit conditions of Faux Pas' and the 'Detection of Faux Pas' dimensions of social cognition. The direct effect of cognitive control on the same tasks was found to be positive and relatively low. Gender was found to affect negatively and low anger recognition. However, no relation was confirmed between emotion recognition and social cognition or between gender and complex social cognition. Moreover, educational level was not found to relate with any one of the other variables in the model (see Figure 4).

Discussion

Indirect speech understanding in adults
The finding that ISUT consists of one factor, namely the 'Understanding of Indirect Speech' factor, indicates that young, middle-aged and older adults use a common mental mechanism - pattern to process indirect speech. However, the way that this pattern is formulated was not totally expected. According to the relevant theory, understanding of irony, humor and sarcasm, as forms of indirect speech, requires two discrete levels of ToM. The ability to go beyond the literal meaning of a sentence mentally, in order to understand that the speaker is not lying but is intending to express something in an indirect way, implies first-order ToM. In order for the speaker's intention either for irony, humor or sarcasm, to be understood, second-order ToM is required [12].The findings of the present study are partially in agreement with the above theory. The model which was confirmed shows that in order to understand these three forms of indirect speech, the abilities to distinguish them from a sincere exchange or a lie and to infer the speaker's correct intention are indeed the ones needed but they are processed in the same level of ToM complexity, as parts of a single dimension - ability of

indirect speech understanding in adults, independently of their age.

As regards the development of indirect speech understanding during the lifespan, this ToM component first appears at about six to eight years of age [48], that is, relatively lately in comparison to other abilities of social cognition. The findings of the present study indicate that adults, at least as regards written forms of indirect speech, have the capacity to distinguish irony, humor and sarcasm from a sincere exchange or a lie, but they find it difficult to properly convey the speaker's intention and understand which specific form of indirect speech is expressed. Specifically, it seems that between the three forms of indirect speech, adults face difficulties in the attribution of irony and sarcasm intention. In particularly, the greatest difficulty lies in the understanding of sarcasm, as the intention for sarcasm was correctly attributed by a very low percentage of participants in this study. Moreover, a large proportion was found to confuse sarcasm with irony. This finding is not surprising, and, despite the fact that sarcasm is a more caustic form of indirect speech and is used to exert a strong criticism, it is a form of irony [49]. Hence, the sarcasm stories used in this study are possibly not the most appropriate tasks to properly reflect the 'stinging' nature of sarcasm.

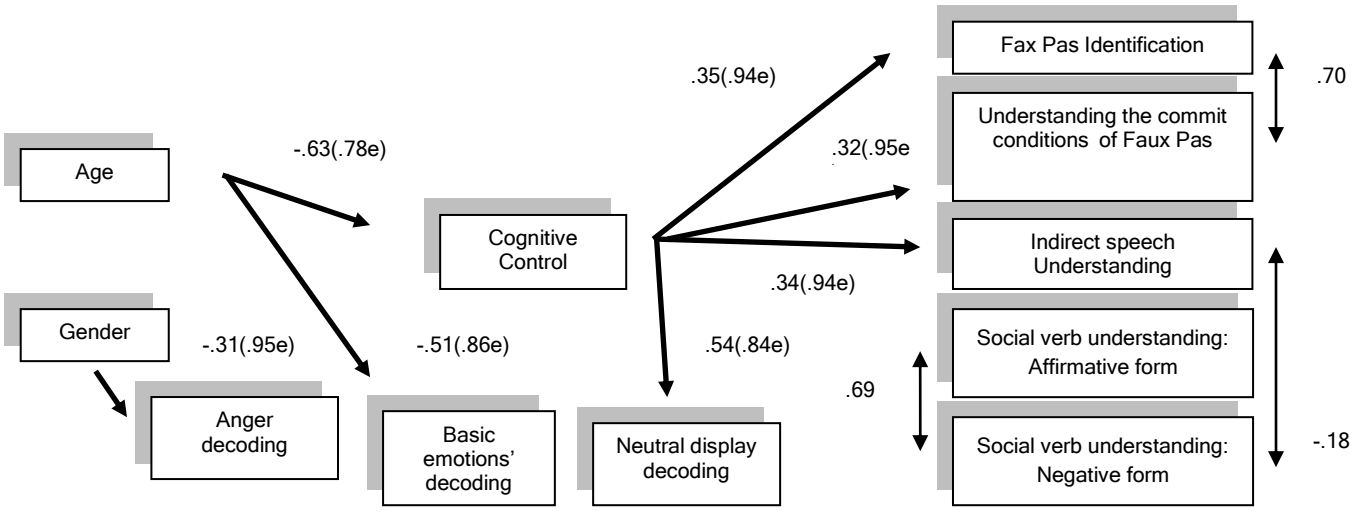

Figure 4. The final path model displaying the relations among age, gender, emotion decoding variables, cognitive control, and social cognition's dimensions (standardized solution).
*All paths and correlations drawn indicate significant associations (p 0.05). **e = measurement error. ***Gender: 1=female, 2=male

Regarding the ability to understand irony, the most of the participants gave a completely wrong answer for the intention of the speaker. In a smaller percentage, participants correctly understood the intention of irony, while the same number of participants was found to confuse irony with humor. Moreover, despite the fact that the findings of this research show that adults have a satisfactory level of understanding humor, many of the participants who answered wrong in this case, confused humor with irony. According to the literature, irony and humor are theoretically considered different forms of indirect speech. However, it has been found that adults often recognize humor elements in ironic statements [50]. In conclusion, it seems that adults, independently of their age, recognize indirect speech but face serious difficulties in understanding the discrete forms of indirect speech [51].

Faux pas understanding in adults

Through the single-factor model, which was confirmed in this case, it seems that in order for a faux pas to be understood, not only the ability to identify a faux pas is required but also the ability to understand the commit conditions of faux pas. Furthermore, it was found that from the five questions that theoretically examine the understanding of commit conditions of faux pas, only three contribute to the understanding of this form of inappropriate speech, in adults. Thus, it seems that young, middle-aged, and older adults process a faux pas in a common way, and the ability to comprehend a faux pas is reflected in understanding the reason for which the inappropriate statements did not have to be said, in the ability to attribute the speaker's intention and in understanding the listener's feelings. Moreover, as the observed variable 'Identification of Faux Pas' and the latent factor 'Understanding the commit conditions of Faux Pas', were found to correlate strongly and positively, it is indicated that the identification ability and the ability to understand a faux pas in depth are distinct but strongly interconnected processes in adults.

The ability to understand a faux pas in typically developing children is firstly observed around nine to eleven years of age [15], and it has been reported that it may still develop during adolescence and adulthood [7]. The performance of the participants in this study demonstrates that adults posses the ability to understand the social blunders in a high level. More specifically, at a much higher rate than average, the participants recognized in all three stories that something awkward was said. Moreover, on the basis of the percentage of participants answered correctly to the questions which load on the factor 'Understanding the commit conditions of Faux Pas', it is indicated that adults have the capacity to infer the listener's feelings and also to understand the reason why the speaker did not have to say this causerie. To a lesser extent, however satisfactory, adults appear to properly understand the speaker's intentions. Although faux pas understanding is considered a complex social cognitive ability, on the basis of the extant literature the performance of healthy adults is expected to be good, as it has been reported that the same ability is maintained even in patients with neurological disorders [16, 52]. Furthermore, it has been found that in studies in which healthy adults participated as a

control group, their performance was very high [53-54].

Social mental verb understanding in adults

Considering the model which was confirmed for the SMVUT, it seems that this complex ToM ability consists of two interconnected dimensions, namely the abilities to understand social verbs in affirmative form and in negative form. The findings show that young, middle-aged, and older adults process social mental verbs in a common way, which, however, varies depending on the form in which the verb is given. Such a conclusion corroborates the suggestion that the processing of affirmative and negative sentences differs, as it has been observed that during their processing different brain areas are activated. Christensen (2009) [47], on the basis of the findings of an fMRI study, has claimed that, through a negation, left premotor cortex exhibits an increased activation, whereas affirmation causes an increased activation in the right supramarginal gyrus. In this vein, it is likely that since these two types of clauses are mediated by different brain areas, they could also be processed in a different way, at the cognitive – behavioral level [47].

Although language significantly affects the quality of social interactions and the performance on tasks that measure various dimensions of social cognition [17], the empirical studies examining the ability to understand social mental verbs in adulthood are considerably limited. In this context, the present study tried to fill the gap that exists as concerns adults' ability to understand the social factor and the 'indeterminate' nature of social verbs. The results indicated that adults do not possess a well-formulated level of social mental verb understanding during the lifespan. This does not mean that they do not understand the semantics or the meaning of social mental verbs. However, it seems that, when they have to make inferences about these verbs, they are based on heuristics or/and pragmatological schemes. Generally, discourse comprehension could occur through top-down processing and also by using the 'real world' knowledge [55]. Furthermore, in order to understand a text, complex representations are used, which are formed by text information and also by the accumulated knowledge [56]. Moreover, in order to comprehend a text, people tend to use situation models, which are multi-dimensional representations of the topic of the text that include information such as space, time, and causal relationships [57]. According to the findings of this study, it seems that adults, due to their need to eliminate uncertainty involved in the information processing system about a social mental verb [58], tend to 'treat' social, nonfactive verbs as factive ones. On the other hand, the high-level performance of the participants, as regards cognitive mental verb understanding, indicates that adults have the ability to understand the factivity and the true event that these verbs denote. Knowing the way in which adults organize their mental lexicon, this finding is not surprising. As mentioned, they seem to be more able to process mental verbs of low uncertainty such as the factive ones, because of their lower-level demands in terms of inference and information processing resources [59].

Age and social cognition: Is there any direct relationship?

One of the main aims of the current study was to examine the direct effects of age on higher-order abilities of social cognition. Although the findings of the existing studies are controversial, the majority argue that older adults exhibit deficits even in simpler forms of social cognition, such as the ability to understand false beliefs [27, 60]. However, in most of the studies it was found that the factor of age does not explain these deficits, as they seem to be mediated fully or partially by other factors, such as executive functions or fluid intelligence [10, 61]. In this line, in the present study it was hypothesized that age would not affect any complex ability of social cognition. This hypothesis (1st) was confirmed, supporting previous findings according to which age is considered simply a time axis, along which various developmental phenomena emerge, and not an interpretive factor for the impairments that older adults face in various cognitive domains [62]. According to the first study examining social cognition in relation to age, it was found that older adults, due to their greater experience, exhibit an improvement in their ability to infer mental states [23]. However, in this study the possible effect of other factors on social cognition performance was not examined. This is a methodological limitation that controverts the validity of the results, as it seems that some factors, such as vocabulary, provide information for the interpretation of older adults' performance. Indeed, in a subsequent research, where older adults did not show deficits in ToM, it was found that the maintenance of this function was attributed to their superior vocabulary abilities. Thus, it has been argued that any deficits that could demonstrate older adults in ToM, are not specific ToM deficits but could emerge due to a general cognitive decline [25].

Gender, educational level, and social cognition

In the present study, the examination of the direct effects of educational level and gender on social cognition confirmed the relevant hypothesis (3rd), as neither educational level nor gender directly affected social cognition. As regards educational level, this result is in line with previous research findings, which showed that this factor does not contribute to the observed older adults' deficits in their ability to infer mental states [36]. However, according to another study, the differences in the performance on social cognition's tasks, which were observed between older adults with high and low educational level, indirectly indicated that high educational level implies higher crystallized intelligence. Hence, this probably constitutes a protective factor for the difficulties that may occur in social cognition across lifespan development [63]. The participants of the current study, as in a recent research of Cavallini et al. (2013) [36], had middle, upper and high educational level. Perhaps, this is a main reason why there was not observed any effect from educational level on complex social cognition examined in this study.

As regards gender, it has been reported that in participants with autism spectrum disorder, it was observed that women performed better on ToM. This superiority of women was claimed that it possibly exists, because women's empathy is in a superior level than men's [64]. In a recent study, where high-school students participated, it was found that gender affects directly and indirectly, through empathy, the performance in a ToM task, with women to display higher performance [65]. As far as we know, the factor of gender has not been examined in relation to its' possible direct effect on social cognition in adults. The results of the current study confirm the respective hypothesis (3rd), demonstrating that gender does not affect directly the complex abilities of social cognition. It is therefore likely that, regardless the differences observed between the two genders in social behavior in "everyday" life [64], men and women in experimental conditions

process the respective tasks in a common way.

Age, gender, educational level, cognitive control, emotion recognition, and social cognition: are there any indirect relations between individual-demographic factors and social cognition?

The path model confirmed, shows that age affects directly and negatively the ability to recognize basic emotions, and indirectly and negatively, via cognitive control processes, the ability to recognize the emotionally neutral expressions. These findings are in line with previous research, as in several studies it was found that older adults are less able to recognize emotions from visual stimuli [66-67]. These difficulties are attributed to the general cognitive function, as it is suggested that the advance of age, accompanied by cognitive decline, causes deficits in recognizing emotions, regardless of their valence [68]. Moreover, this model shows that gender affects directly the ability to recognize anger, as women's performance was significantly better. Differences between the two genders in favor of women are observed since childhood and continued in the period of adulthood [69]. It has been supported that these differences are probably interlinked with gender differences observed in the functional organization and architecture of the brain structures, which are involved in the control of emotions [70, 71].

Interestingly, as regards social cognition, age appears to affect indirectly and negatively the abilities to identify and understand indirect speech and faux pas, through its' effect on cognitive control. Hence, it could be suggested that cognitive control mediates the relation between age and social cognition, and, specifically, between age and the dimensions associated with affective ToM (2^{nd} hypothesis). This finding contradicts those of another study, according to which age was found to affect only those abilities that are related to cognitive ToM [60]. However, at least one study had similar results. In this case, age was found to negatively affect only the dimensions of social cognition in which processing of affective elements was needed. It has been suggested that possibly such a finding was observed due to the association of these abilities with higher memory load [65]. Moreover, it could be argued that as affective dimensions of ToM overlap with cognitive empathy [35], it is likely that the negative effects of age on those abilities could be attributed to deficits in cognitive empathy observed in normal aging [72].

In conclusion, the present study contributes to the literature in terms of providing findings about the difficulties which adults have in sarcasm, irony and social mental verb understanding. Moreover, the findings confirm the conclusions of the existing research, in terms of revealing the important role of cognitive control in social cognition: it was found that the higher-level abilities of social cognition that combine cognitive and affective ToM components, are negatively affected by age, but this effect is fully mediated by the difficulties that older adults face in cognitive control tasks.

However, there are some limitations in the study. The restricted nature of the sample should be noted with regard to the number of participants in each age-group. The limited number of dimensions of social cognition examined, the non-dynamic tasks used, the inability to associate behavioral performance with more objective indices of cognitive performance and neuroimaging data should be also mentioned. Moreover, a main limitation is the cross-sectional design of the study. It is unknown if the same pattern of results would be obtained if the same persons had repeatedly been measured at different age. Generally speaking, more rigorous methods and longitudinal design are needed to examine in depth the effects of age on social cognition.

The authors declare that they have no conflicts of interest.

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The relationships of Theory of Mind, cognitive control and memory function in Mild Cognitive Impairment: A research proposal

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Abstract

Aim: The study aims at investigating the relationships among cognitive control (Cc), memory functioning and Theory of Mind (ToM) in Mild Cognitive Impairment (MCI) patients, and examining the predictive power of these psychological constructs and their relationships for conversion to dementia. **Method:** The study has complex design (cross-sectional and longitudinal). The sample of the cross-sectional phase will comprise three groups matched for gender and age: a. "healthy" older adults, b. older adults with risk factors for vascular disease development, and c. older adults diagnosed with MCI. The last two groups will be examined at three different times (longitudinal phase). The participants will be measured with tests assessing a series of different dimensions of memory function, Cc, and ToM. **Results:** Multi-group and non-recursive path analysis will be applied to the cross-sectional data, to reveal the differences in ToM, memory, and Cc in the three groups, and to create an initial profile of the relationships among the three constructs measured, for each group. Latent Growth Curve Modeling will be used to find the trajectory of change of these profiles in the last two groups. **Conclusion:** Based on the findings from the cross-sectional phase, a different pattern (profile) of relationships among ToM, memory and Cc in each group would emerge. Based on the longitudinal findings, possible changes in these profiles would emerge that could be associated with conversion το MCI and dementia, for older adults with vascular risk factors and MCI patients, respectively.

Introduction

Mild Cognitive Impairment (MCI)

Currently, the pathology of dementia is typically diagnosed at a stage when neural degeneration has already progressed and its course is irreversible [1]. In the past decade [2] the term "Mild Cognitive Impairment (MCI)" was introduced to describe the trajectory of decline in cognition that is identified with dementia. The ability to diagnose MCI and form a prognosis for it is deemed extremely important, especially at its earliest stages, during which it is assumed that it would be possible to intervene in the development of the cognitive decline and delay its adverse effects [3]. The criteria for the diagnosis of MCI were initially laid out in 1999, by Petersen and colleagues [4]. A basic criterion was the subjective assessment of impairment in "everyday" memory functioning, and its objective clinical assessment was a prerequisite. However, according to the original definition of MCI, the other cognitive functions remain at normal levels, "everyday" functioning is relatively well-maintained and the criteria for a diagnosis of dementia are not met. In 2004, the same researchers [5], based on clinical observations, revised their criteria and distinguished MCI subtypes. In summary, MCI is classified as amnestic MCI when it presents primarily with memory deficits, while, when the primary deficit is not in the memory domain, but one or more other cognitive functions are impaired, it is classified as non-amnestic MCI. Consequently, the umbrella term "MCI" includes a non-homogenous group of symptoms at the cognitive level. Its incidence affects between 3% and 42% of the typical population, and the most common age-range for its emergence is 65 to 85 years. As pointed out [6, 7], due to the wide heterogeneity of symptoms, individuals diagnosed with MCI may present deficits across several different cognitive domains, such as language, executive functions, attention, and visuo-spatial perception. In order for a diagnosis of MCI to be given, a series of cognitive functions and abilities must be assessed with neuropsychological tests, and a deficit in performance must be established by at least 1.5 Standard Deviation, compared to the performance expected based on the examinee's age and educational level [5]. In a recent study [8], it was concluded that 60% of individuals diagnosed with MCI will eventually fall to Alzheimer's-type dementia, while 30% will fall to vascular dementia. Despite the increased risk of transitioning from MCI to some type of dementia syndrome, a noteworthy percentage of persons with an MCI diagnosis remain at the initial stage and do not progress to dementia [9]. Also, it is possible for a percentage of patients to return to performance levels that are normal for their age-group and educational level [10].

MCI and memory function

As has already been pointed out, one of the diagnostic criteria for MCI are memory deficits [11]. Deficits in "episodic memory" defined as the memory of personal experiences occurred at a particular time and place, are often evident in persons diagnosed with MCI [12, 13]. Specifically, there are recent studies [14, 15] that examined memory deficits, as these were reflected in the patients' daily lives, and correlated them with impairments in episodic memory. These studies [15] posit deficits in "prospective memory" -namely, the form of episodic memory that involves remembering to perform a planned action or intention at some future point in time- as a characteristic of patients who will eventually develop dementia, as well as in "autobiographical (retrospective episodic) memory" [16-20]. Moreover, there are some studies that

indicate the presence of deficits in “semantic memory” that refers to general world knowledge that has been acquired by a person, as manifested through the “naming test” [21].

MCI and cognitive control (Executive Functions)

Executive functions are cognitive processes that control thought and action. At the neural level, they are supported primarily by the prefrontal cortex [22]. Compared to lower-order cognitive functions, executive functions are higher-order processes [23], mainly in terms of their role to coordinate the other dimensions of cognition. Based on the structural validity of the tasks examining executive functions that are currently being administered, the best-known such functions are: updating primarily of the working memory with any new information, which must be incorporated into existing knowledge and reconfigure it (updating - monitoring); the ability to shift between different tasks or rules (task switching); the ability to inhibit information that is irrelevant to the task that the person is currently engaged in (inhibitory control); and long-term planning [24, 25]. In cognitive neuroscience, the umbrella term used to encompass all executive functions including the interactions between them is “cognitive control” [26-29].

Whereas, until recently, it was memory deficits that supported a diagnosis of MCI, today it is proposed that deficits in executive functions may be indications of the condition [30]. According to a review of the existing literature, many patients with MCI deal with problems in cognitive domains other than memory [31]. Existing studies maintain that such deficits, with performance below the expected for age and educational level, appear at a stage before clinical dementia and may even predict the transition to it [32]. The supervisory attentional control system, working memory, verbal and visual organization, planning, critical ability and reasoning were recently studied [33] and deficits in these domains of cognition were linked to everyday activities and, by extension, to the autonomy and productivity of patients diagnosed with MCI. Moreover, a meta-analysis [34] maintains that executive deficits in MCI appear equally frequently, or even more frequently, than memory deficits.

MCI and Theory of Mind (ToM)

Theory of Mind is the ability to understand other people’s intentions and desires, which may be the same or different from one’s own [35]. Based on the findings of related research so far, this ability can be distinguished into two types: cognitive and affective. Cognitive ToM refers to the attribution of opinions, thoughts or intentions to other people [36]. Affective ToM refers to the attribution of feelings, emotional states and moods to other persons [36]. There are several recent studies that deal with the neuro-anatomical underpinnings of ToM, which primarily involve the prefrontal cortex and, specifically, the orbital frontal regions and the medial prefrontal cortex [37 – 39].

In more recent literature, we come across studies on Theory of Mind in MCI. However, while extensive research has been done on dementia syndromes and deficits in ToM [40, 41], to our knowledge only one study deals with ToM deficits in persons diagnosed with MCI [42]. In this study, the findings appear to agree with findings for sufferers of Alzheimer’s-type dementia: compared to healthy individuals, MCI patients perform worse on complex ToM tasks, while their performance on tasks that assess first-order ToM is similar to normal participants [42]. Several researchers maintain that the deficits that present in ToM are secondary and dependent on executive functions and memory [43, 44]. However, the existing literature on this topic is extremely lacking.

Regarding, in particular, basic emotion recognition, which appears to be a primary, relatively instinctive dimension of affective ToM, studies have shown differences in performance between normal participants and participants suffering from MCI [45], with the latter performing worse than the former. This finding is also supported, to some degree, by the deficient performance regarding positively-valenced emotion decoding from dynamic visual cues, of dementia sufferers compared to “healthy” older adults [46, 47].

The proposed study

Dementia is a condition with serious social and financial demands and burdens, with a rapid increase of its incidence in the population and, so far, without effective cure. The entire effort to manage the condition is currently focused on prognosis and prediction. According to what is mentioned above, MCI is linked to an increased risk of transition to a dementia syndrome. Due to the importance of the prognosis for the early intervention in the course of dementia and in the preservation of the patient’s autonomy [48], recent studies have focused on the early diagnosis of MCI. Their goal is to develop new, direct, aggressive and targeted interventions, which will have positive effects in regards to the non-transition of MCI to dementia, and also to the more mild evolution of the dementia syndrome, in case it manifests [49]. The latest studies [50] support groups of neuropsychological and behavioural similarities in persons diagnosed with MCI and refer to neuropsychological profiles. In the same vein, it is known that the impairment of executive functions commences long before MCI becomes symptomatic [30].

Along the same lines, several studies have linked non-diagnosed vascular pathology with cognitive impairment. It is reasonable to maintain that since vascular disease affects the brain, it also affects cognitive functioning [51]. Specifically, it appears that vascular disease causes brain atrophy and loss of neural synapses, resulting in accelerated cognitive aging [52]. In fact, the theoretical approach of the “vascular hypothesis of cognitive aging” [53, 54] posits that basic risk factors for the emergence of vascular disease, such as hypertension, hyperlipidemia, and diabetes mellitus, affect cognitive functions that are supported by the frontal brain regions, such as working memory [55, 56]. However, the physiological changes that underlie cognitive impairment are still under investigation [57 – 59].

Considering the aforementioned theory and evidence, the importance of establishing a complex index that will quantify impairment in specific, higher-order or not, cognitive functions, and will be linked to the emergence of pathology while the person’s behaviour still remains normal, is one of the issues on which there is a lack in the existing literature and for which clinical practice is seeking solutions.

In this light, the proposed study aims, first, to investigate the differences among three groups of older adults (“healthy” older adults, older adults with risk factors for the development of vascular disease, and older adults diagnosed

with MCI) in regards to three dimensions of cognition –Theory of Mind, memory function, cognitive control– and to the pattern of relations between these dimensions (cross-sectional design).

Specifically, based on the existing literature, the following *hypotheses* are formulated: 1) The three groups of older adult participants shall have statistically significant differences in regards to cognitive control (executive functions). As regards memory function, the performance of both the "healthy" group and the group with risk factors for vascular disease is expected to have statistically significant differences from the performance of the group with MCI. Similar differences, at the level of "trends" and not necessarily statistically significant, are also expected for ToM. 2) The pattern of relations between ToM, cognitive control and memory function is expected to differ in the three groups of older adult participants. That is because any deficit in performance in one or more cognitive dimensions in any one or more of the older adult groups may likely lead to a reconfiguration of the relations between these dimensions, due to the efforts of the cognitive system to adapt to the new, diminished levels of brain functioning.

On a second level, the proposed study aims to examine the trajectory of change in the three cognitive dimensions and their relational pattern, in two groups of older adult participants: a. older adults with risk factors for vascular disease development, and b. older adults diagnosed with MCI. In this way, it could emerge whether and to what extent any changes in the measured variables' trajectories, during a year and a half, are related to a transition to MCI and dementia, for the group with vascular risk factors and for the group with MCI, respectively (longitudinal design).

Based on the existing literature, the following *hypotheses* are formulated: 1) In regards to the performance of the two groups, through repeated (three) measurements, the older adult participants with an MCI diagnosis shall have lower performance than the participants with vascular risk factors in memory function, cognitive control and ToM tasks. Furthermore, the trajectory of performance change in these tasks shall differ between the two groups, with the trajectory of change presenting a greater and sharper decline in older adults diagnosed with MCI, compared to older adults with risk factors for vascular disease development. 2) In regards to the pattern of relations among the three cognitive dimensions, longitudinally, it is expected that changes in this pattern of relations shall be observed primarily as effects of the previous measurements of memory and cognitive control on the subsequent measurements of Theory of Mind.

Method

Samples

Cross-sectional phase. The sample in the proposed study shall consist of three different groups of older adults, matched for gender, age and educational level. Each group shall be composed of 50 participants. All participants shall be at least 65 years old or older, with at least six years of schooling and Hellenic as their native language. The first group shall be composed of "healthy" participants who, based on recent blood tests, should be at no risk for vascular disease development. Such risk factors are considered the following: hypertension, hyperlipidemia, diabetes mellitus, smoking, and systematic alcohol use. Also, potential participants should not have any symptoms of clinical depression, history of psychiatric disorders or history of addiction, and cognitive impairment. The second group shall be composed of participants with one or more of the above-mentioned pathological biomarkers (hypertension, hyperlipidemia, diabetes mellitus), based on recent tests and diagnoses by their personal physicians. Besides that, participants in this group should also be in normal cognitive and mental health condition. The third group shall be made up of older adults with a diagnosis of MCI, which shall have been diagnosed following a neurological, neuroimaging and neuropsychological assessment. Their cognitive impairment should not be the result of an emotional, psychological or other physical disorder. Their "everyday" functioning should be preserved and they should not be eligible for a diagnosis of any type of dementia.

Longitudinal phase. Subsequent to the study, at the longitudinal level, two additional measurements have been planned, which shall occur one at 12 and one at 18 months later. At each measurement, half of the participants in the group with risk factors for vascular disease development shall be tested (n = 25), as well as half the participants from the group of persons diagnosed with MCI (n = 25), from the initial sample of the cross-sectional phase. During both re-evaluations, the neuropsychological assessment adopted in the cross-sectional phase will be repeated; also, biochemical tests will be rerun, as well as new neuroimaging tests.

Instruments – Measurements

The neuropsychological screening measures that will be used to assign participants to each of the three groups –in addition to an existing diagnosis, where necessary– are: for the assessment of their general cognitive status, the Mini Mental State Examination [60, 61], and the Montreal Cognitive Assessment [62, 63]. Furthermore, participants will be administered the Geriatric Depression Scale-15 [64, 65], in order to exclude persons with depressive symptomatology. From the Boston Diagnosing Aphasia Examination [66], the "auditory perception" subscale will be used to broadly assess general ability to comprehend simple and complex sentences. From the Rivermead Behavioural Memory Test [67, 68], the subtest "7 – Faces", in a slightly transformed version, will be used to assess face perception.

The main neuropsychological assessment will be implemented with the administration of a battery of tests to assess memory function, cognitive control, and Theory of Mind. To measure memory function, the following instruments have been selected: for retrospective episodic memory, the Doors and People battery [69] and the related subtests of the Rivermead battery; for the assessment of prospective memory, the Belongings and Appointment subtests from the Rivermead battery will be used. In order to assess working memory, the Working Memory Index from the WAIS IVGr [70, 71] has been selected.

To measure main executive functions, that is inhibitory control, task switching, updating-monitoring and planning, the following instruments have been selected: the Trail Making Test A & B [72,73]; the Colour-Word Interference Test, the Design Fluency Test, the Verbal Fluency Test (semantic and phonologic fluency with or without rule switching), and the Tower Test from the Delis-Kaplan Executive Function System battery [74].

To assess ToM, the following tasks have been selected: the Social and Cognitive Mental Verbs subtask from the Natsopoulos' ToM battery (75); the Proverbs from the WAIS IVGr Verbal subtest [70 71]; and the Social Inference – Minimal subtest examining sarcasm understanding, from The Awareness of Social Inference Test [76]. Finally, to measure the ability to recognize basic emotions, as an underlying psychological construct for the development of the affective dimensions of ToM, the Emotion Evaluation subtest, also from The Awareness of Social Inference Test will be used.

Clinical neurological examination. Both in order to form the participant groups and parallel to the neuropsychological batteries, the participants will be submitted to neurological examinations, in order to exclude other potential neurological diagnoses that could affect their cognitive profile, and also in order to correlate the clinical points of the neurological examination with the results of the neuropsychological tests.

Blood biochemical analysis. The biochemical analysis will also be important for the assignment of the participants in the three groups, and it will be repeated in the two phases of the research design, in order to investigate the relation of the biomarkers with cognition and the trajectory of cognitive impairment.

Neurophysiological examination – Event-Related Potentials (ERPs). ERP measures have been proven to be sensitive cognitive indicators for the examination of patients with a variety of cognitive disorders, such as dementia. In the longitudinal phase of the proposed study, the participants would also be submitted to ERP measures, in order to assess longitudinal changes in specific dimensions of cognition.

Design and Procedure

According to the design, the study will be carried out in two phases. In the first, cross-sectional phase, all older adult participants in all three groups will be tested in all tasks. In the second, longitudinal phase, half of the participants in the group with vascular risk factors and in the group with MCI diagnosis will be reassessed, at 12 and 18 months after the initial assessment.

Testing will take place over two sessions due to its long duration and to avoid the fatigue factor affecting performance. The order in which the neuropsychological tests will be administered will be alternated, in order to avoid any potential sequence effects. Sessions will be held in the morning and no more than 7 days apart; participants must get a good night's sleep the previous night and appointments will be made by arrangement. Participation in the study is voluntary. All the potential participants will have to sign an "informed consent" form in the beginning, in order to be able to proceed with the examination. Participants may withdraw from the study whenever they wish.

Anticipated Results

Cross-sectional design. For data analysis, the SPSS Statistical Package for the Social Sciences, version 21 [77], will be used. The analyses to be made to trace differences between the "healthy" older adults, the older adults with vascular risk factors, and the older adults with MCI, in regards to their performance in the memory tasks, as well as in the tasks measuring executive functions and ToM, are: a) mixed-design analysis of variance (mixed ANOVA), with "group" as the between-subjects factor and "condition" (this term is used to refer to the different conditions composing each test) as the within-subjects factor. In order to interpret any statistically significant interactions, we will run repeated measures ANOVAs, multivariate ANOVAs, and one-way ANOVAs. Next, in order to reveal differences in the pattern of relations among the different tasks and their conditions, analyses will be performed with the EQS statistical program [78]. Specifically, structural equation modelling (SEM) techniques will be applied to covariance matrixes. In particular, using path modelling, the directed relations between multiple constructs will be examined [79]. In addition to the basic path analyses, a series of multi-group path analyses will be performed, to trace and compare any eventual differentiated patterns of directed relations among variables [79], for every group in the cross-sectional phase's sample.

Longitudinal design. The EQS statistical program [78] will be used to analyse the data. In order to assess changes over time in the performance of older adult participants with risk factors for vascular disease development and older adults diagnosed with MCI in memory tasks, executive functions and ToM, the Latent Growth Curve Modelling technique will be applied to the data. This technique will reveal any eventual non-linear changes in the cognitive dimensions under investigation. Also, this provides the opportunity to compare the trajectory and size of changes in the groups under study and in each participant-member of these groups. Next, in order to capture the dynamic pattern of relations among the dimensions of cognition for every group of the longitudinal phase's sample, confirmation will be sought of a series of Autoregressive Latent Trajectory (ALT) models [80].

Discussion

The proposed study was designed in order to examine early cognitive impairment in older adults, by cross-sectionally comparing three groups of older adults ("healthy" older adults, older adults with high risk for developing vascular disease, and older adults with a diagnosis of MCI), along three dimensions of cognition. For this purpose, a longitudinal study was also designed to assess the trajectory of impairment of the same cognitive dimensions in two groups of older adults (older adults with high risk for developing vascular disease, and older adults with a diagnosis of MCI).

The 1st hypothesis of the proposed study suggests that the group of older adults diagnosed with MCI shall have the worst performance in tests of episodic memory, compared to the other two groups, which will not differ statistically between them. Such a find is interpreted based on the existing literature and research completed so far on MCI, which supports that considerable decline in the episodic memory system is a clear indication of the development of MCI.

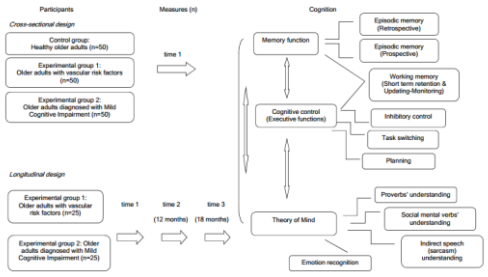

Figure 1. The design of the study: subsamples, times of measurement and cognitive dimensions to be examined in the cross-sectional and longitudinal phase

The same hypothesis (1st) proposes that there will be differences in the performances of the three groups of older adults, in regards to cognitive control. In particular, based on the existing literature, the proposed study is expected to corroborate that older adult patients diagnosed with MCI perform worse, compared to individuals with high risk for vascular disease and "healthy" participants, in tasks that require updating, task switching, a combination of task switching – inhibitory control, and planning. Moreover, participants at high risk for vascular disease shall perform worse than "healthy" older adults, mostly in the more complex cognitive control tasks, such as the combination of task switching – inhibitory control and planning. These variations can be linked to losses in episodic memory in MCI, and also to the more advanced and perhaps also accelerated rate of degeneration of the frontal brain regions, due to underlying vascular pathology, both in individuals with high risk for developing vascular disease and in patients diagnosed with MCI, compared to their "healthy" peers [12, 52].

According to the literature that maintains that ToM is supported – at least in part and in regards to specific components thereof – by executive functions, the performance of the two groups, older adults with high risk for vascular disease and older adults diagnosed with MCI, on dynamic ToM tasks, such as comprehension of indirect speech, shall be lower than the corresponding performance of the "healthy" older adults. This shall not be due to a decline in the ability to comprehend indirect speech itself, but to a decline in executive functions. Additionally, in ToM tasks which pertain to the individual's previous experience, such as the task of understanding social mental verbs, it is possible that older adults with a diagnosis of MCI shall fare worse than the other groups, due to the more extensive decline in their autobiographical memory (retrospective episodic memory).

On the other hand, if the ability to recognize emotions is, indeed, a primary and instinctive dimension of ToM, the proposed study is likely to find that this ability does not differ between the three groups of older adults. Conversely, any differentiation in the recognition of specific emotions, such as happiness, may be interpreted based on psychosocial theories on emotional aging. Such theories support that the tendency towards positive affect is a choice made by the older adult which, however, can only be made when it is supported by a relatively powerful system of cognitive control [81].

Variance in performance in the subtests for each one of the three dimensions of cognition is what will determine and differentiate the pattern of relations of the three dimensions within each group (2nd hypothesis).

In regards to the longitudinal stage of the proposed study, the 3rd hypothesis maintains that both the participants with elevated risk for vascular disease and the older adults with a diagnosis of MCI shall perform generally worse along all three dimensions of cognition, in each subsequent evaluation. This is because the underlying brain damage is expected to deteriorate in the participants of both groups. However, supposing that MCI is a pathological condition that can be diagnosed at the neuropsychological, neuroimaging, and biochemical level, more clearly than the corresponding damages caused by elevated risk factors for vascular disease, it is reasonably expected that in the comparison between them, patients diagnosed with MCI shall fall short of the other group. And this shortage will potentially be displayed not only as a "quantitative" difference in their performance, but will also be depicted as a different curve of the trajectory of cognitive decline. Indeed, for some of the patients diagnosed with MCI, this curve may show a rapid decline in cognition, which could be linked to the transition to dementia. In this case, the common characteristics of such individuals could be revealed, based on all of their measurements. It would be of particular interest if a sub-group of older adults with high risk for vascular disease appeared to differ negatively in regards to the curve of their cognitive decline, compared to the average curve for their entire group. This would essentially allow the depiction of a course of decline linked to a transition to MCI and, subsequently, a recording of the common characteristics of persons who follow this negative course [54].

Variance in repeated performance in the subtests for each one of the three dimensions of cognition is what will determine and differentiate the dynamic pattern of relations of the three dimensions within each group (4th hypothesis). Based on a study of these patterns, conclusions could be drawn regarding the trajectory of degradation of the cognitive dimensions being studied, as well as the compensative strategies employed by the cognitive system in order to adapt and to remain – in part, and as much as possible – functional, even in conditions where it is irreversibly degraded [49].

Based on the anticipated findings, the proposed study will attempt to formulate an "index" that will quantify early cognitive impairment and will be linked to the potential manifestation of pathology at an early stage, when intervention will be possible and the person's behavior will remain relatively intact. Based on the findings of the longitudinal phase, it is expected that the dynamic pattern of relations of three dimensions of cognition, which are essential to "everyday" life, shall be revealed; in this way, it will become relatively possible to predict the transition from the state of being at high risk to develop vascular disease to the state of MCI, and from that to dementia.

Limitations of the study and future research

A basic limitation for this study is the sample size. Although the number of participants in each group permits the application of the proper statistical techniques, a larger number of participants in each group would ensure greater reliability and validity for a future study. The use of advanced neuroimaging techniques, which is not considered possible within the framework of this study, could help decisively, both in coming up with a more accurate differential diagnosis in regards to assigning the patients - participants to each group, and in the more accurate assessment of cognitive impairment based on various brain measurements. The proposed study focuses on the neuropsychological evaluation of only three dimensions of cognition. Beyond adding measurements pertaining to a series of ToM abilities that are not included in the design of this study, a larger study could also include other dimensions of cognition and metacognition. Furthermore, it could evaluate dimensions of social cognition that are strongly interconnected with ToM, such as empathy. Finally, the longitudinal phase could include more times of measurement and follow older adult participants even up to their death, if the funds could be secured for the development of such a study in the future.

The authors declare that they have no conflicts of interest.

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Can the Mini Mental State Examination detect cognitive changes in childhood and aging?

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Abstract

Objective: Human brain undergoes significant changes in both its structural architecture and functional organization across the life span. The pattern of age-related shifts and cognitive decline in neurocognitive pathological aging and the research findings for retrogression in childhood are discussed with main aims 1) to investigate the effect size of general cognitive changes in elderly and children (first-last grade) through their performance in a brief screening test and 2) to compare their performance in some later acquired cognitive abilities. **Subject and Methods**: Our total sample was 265 participants, 177 (first and last grades) children and 88 elderly (mild Alzheimer' disease -mAD and non demented) recruited randomly from schools and 2 hospitals respectively who were administered a couple of physical, neuropsychological and neuroimaging examinations. **Results**: The results indicated that first grades children showed better and large effect size performance compared with mADs in general cognitive function, and other cognitive abilities as time orientation, attention, language and recall. However, last grades children showed the same performance with the non- demented elderly in the general cognitive state and significant better than them in recall. **Conclusion**: Reliable and validated brief screening tests can give quickly crucial information for the general cognitive state and the separate cognitive abilities in young children and mAD in order to use it for the management of elderly.

Introduction

The human brain undergoes significant changes in both its structural architecture and functional organization across the life span. Changes in brain structure occur in parallel with changes in cognition and basic functions such as sensory and motor processes seem to mature first, though basic language skills and spatial attention mature next [1]. There are 3 types of theories for age-related shifts related to cognitive functions: 1) the dedifferentiation hypothesis which claims that cognitive variables and abilities become less distinct with increased age, 2) the disintegration hypothesis indicates that cognitive variables maybe become more independent of one another during advancing aging because of weaker interrelations among cognitive variables and 3) the equivalent-structural-influences hypothesis which suggests that the advancing aging is associated with cognitive decline without appreciable shifts in the level of which cognitive change happens, as its accepts that there is little or no relation between age and the level at which change operates [2].

The above theories arose from the researches questions for cognitive shifts in aging which can be summarized to 1) what abilities are related to age, 2) how many distinct influences are between age and cognitive functioning, 3) if the differences between people increase with advancing age, 4) which are the variables that are mediating for the discrepancies between cross-sectional and longitudinal age comparisons of cognitive functioning, and 5) what statistical methods can be used to identify causes of age-related influences on cognition [3].

The age related changes can be attributed to 3 factors a) a single general factor of cognitive change, above and beyond any ability-specific changes could be occurred, b) the number of distinct influences contributing to both age differences and age changes in cognitive functioning which is smaller than the number of variables exhibiting age relations and c) the examination of a variable in the context of other variables in order to determine the extent to which the age-related effects on a given variable are independent of age-related effects on other variables. Although there are large age-related declines in mean performance in every variable, the magnitude of the individual differences in performance across this age range was found nearly constant. Different age trends was found for the same persons at different ages, and for different people at different ages. Some of the discrepancy between cross-sectional and longitudinal age trends in cognitive functioning is likely attributable to prior practice [3].

Longitudinal change in cognitive test scores and abilities was systematically more negative as age increased and is more quantitative than qualitative in the nature of cognitive change among healthy adults from about 20 to 90 years of age. Test scores reflect the sum of influences origin at least at 3 levels, namely, a proportion of the variance in change could be inferred to be specific to the test score, another one could be inferred to operate at the ability level, and a third one could be inferred to operate at the level of the g factor [2].

Many studies argue that an appreciable cognitive decline begins between 50 plus and 60 [4-6] and that little cognitive decline occurs before 60s. Memory and speed seem to be highly sensitive to age (especially after 60s), though vocabulary and general information do not seem to have a significant decline. The most affected cognitive functions before 55 years old seem to be the reasoning and spatial orientation [5], however, the speed of processing information begins to decline earlier about 45 years [7,2]. According to the neurocognitive disease due to Alzheimer's disease literature refers that the cognitive state of an Alzheimer's disease patient retrograde to the first grades of elementary school and even further, to the levels of kindergarten [8,9,6].

The performance of the rapid cognitive development during childhood seems to continue from 7 to 12 years old including mainly language, memory, reasoning. However, cognitive decline in aging seems to be referred to the most demanded cognitive functions as memory and reasoning. Many researches [2, 10, 6] argue that the crucial cognitive decline takes place after the 70s and go on to 80s and 90s. Specifically, the memory decline is 4 time greater after 70s [4] or in other words from 3.3 points in the Mini Mental State Examination (MMSE) [11] after the 70s to 6.9 for the 80s [6]. Gomez-Perez and Ostrosky-Solis [12] examined the development of both attention and memory measures across a wide age range (6-85 years) and found that all attentional factors change faster than the memory factor, as the attention score increased by one point every 6-7 years, whereas the memory factor score changed by one point every 16 years. Variety of verbal learning and memory measures was found to be improved with age, with the exceptions of proactive interference and delayed recall [13].

But what about cognitive developmental changes in children? Typical development children almost always perform poorer than adults without cognitive deficits on complex cognitive tasks. However, it is difficult to specify whether the activation differences are age related or simply reflect a performance difference [14]. Some of the brain regions show differences attributable to age, independent of performance [15] e.g., the executive functioning is considered as the most crucial component underlying development. Memory changes and their relationship with other cognitive abilities e.g., attention, has educational, diagnostic and remedial applications in childhood [16], as well as in aging. A clear and consistent developmental enhancement has been also found of immediate and delayed recall and learning [13, 17] though working memory is a reliable predictor of general cognitive ability which grows steadily during childhood [18]. At certain ages memory performance seems levels off, e.g., the most memory measures are stabilized from 11 [13] to 14-15 years old [17]. There are many explanations which are accounted for the developmental trend of improved memory performance, as general knowledge about the world, language knowledge, or an expertise in a specific domain [7], using better memory strategies by older children [16] or changes in meta-memory [19]. So during early childhood cognitive abilities are undifferentiated, though are differentiated at adulthood and again become undifferentiated in old age [20]. Considering the above theory, attentional difficulties in younger children could be expressed (and misdiagnosed) as memory difficulties or specific attentional difficulties could be associated with specific verbal memory difficulties. Many of the relations initially found between the memory and attention measures are mediated by age. Associations between memory and attention measures that obtained are found primarily in early age groups (8–12) but not in later age groups (13–17). So there is complexity of attention and memory interrelations and how they are modified by age [21]. From a clinical perspective, attention performance at an early age but not at a later age could predict memory performance, and vice versa. Attention and memory are also related to processing speed [22] which is increasing with age. Speed of rehearsal affects the storage in short-term memory, indicating that there is a rapid decay of information in that store [21]. Increased speed may enable a faster switch between processing and storage of these decaying memory traces, thereby improving recall [23]. Speed of rehearsal, speed of retrieval, and the use of rehearsal were the most salient measures that changed with age in phonological short-term memory [16]. It has been argued that speed and capacity are related, since faster processing enables storage of a greater amount of information [24]. Speed also enables faster and more efficient encoding [25].

Except of the above researches there are others that indicate that what seems to develop with age is the ability to hold response competition in check when it occurs, and remove inhibition when the target response is selected [26]. So understanding the normal progression in early and old childhood and aging we will have a significant impact in determining the biological substrates of clinical disorders and mainly targeting effective interventions [27].

Summarizing, crucial cognitive changes in childhood take place from 7 to 12 years old and during the transitional period (56 to 65) from adult to elderly and are established after the 66th year. The cognitive decline in elderly is depicted even in brief screening tests e.g., MMSE and the distribution of its scores demonstrates a wider range of scores with increasing age. The years of typical education should be a crucial variable for the quality of the cognitive changes, even though participants with more than 9 years of education did not seem to have significant differences in the MMSE scores between them [28,6]. Furthermore, a variety of influences on cognitive functioning associated with changes in the social and cultural environment are taking place. These are called as cohort effects. Even though several research findings appear more consistent with the retest interpretation of longitudinal trends than with the cohort interpretation [4].

Considering the previous research findings, the aims of our research study were 1) to investigate the effect size of cognitive changes performance between first grade (7-9.5 years old), last grade children (aged 10-12) and elderly (> 65 years old demented and non demented) in order to compare the cognitive development and cognitive decline performance in childhood and aging respectively using a brief screening test, the MMSE and 2) to compare groups performance in the MMSE items related with some crucial later acquired cognitive abilities (e.g., orientation, attention, language and memory) in order to use this knowledge for managing elderly people and constructing psychoeducational programs.

Subjects and methods

We recruited randomly 265 not institutionalized Greek participants, aged from 7-12 and 65-87 and divided them into four groups. The first one comprised of 80 typical development (without mental, psychiatric or learning disabilities) young children who were attending the 2nd, 3rd and 4th grade of the elementary school (MEAN Age=8.06, S.D=0.9, range=7.0-9.5 years old). The second group comprised of 97 typical development older children who were attended the 5th and 6th grade of the elementary school (MEAN Age=10.7, S.D=0.8, range=10-12). Both of these groups were recruited randomly from elementary schools of the mainland and island Greece. The third group consisted of 43 non demented elderly (mean age=72.39, S.D=5.3, mean education=9.6, S.D.=4.2) and the fourth of 45 mild Alzheimer's disease patient (mean e=75.0, S.D=6.9, mean education =8.2, S.D.=3.8) (table 1).

Table 1. Demographic characteristics of the sample, means and s.d *M-F=Male-Female

Participants	N	Sex	Age		Education		MMSE	
		M-F*	Mean	S.D	Mean	S.D	Mean	S.D
Young Children	80	33-47	8.06	0.9	2.4	0.9	24.98	3.3
Old Children	97	54-43	10.7	0.8	4.9	0.9	27.61	1.9
Total Children	177	178	9.38	0.85	3.65	0.9	26.29	2.6
Non Demented	43	21-22	72.3	5.3	9.6	4.2	27.59	2.0
Mild Demented	45	23-22	75.0	6.9	8.2	3.8	20.02	3.7
Total Elderly	88	88	72.5	7.6	8.8	4.0	23.80	2.8
Total	265	132-133	39.9	3.5	6.2	2.5	25.05	2.7

The demented patients were outpatients of the B Internal Medicine of the Medical School of the Aristotle University of Thessaloniki, Thessaloniki, Greece and the Neurologic Clinic of the General Hospital of Agios Pavlos, Thessaloniki, Greece, though the non demented controls elderly were visitors of all the departments of the hospitals and other elderly who were responded to an invitation for a memory testing after a briefing about dementia risks in aging. Our scientific team consisted of expertise clinicians e.g., neurologists, geriatrician, neuropsychologists, pediatricians and radiologists who gave their consensus for the diagnosis of dementia and the absence of other mental health or neurodevelopment disorder based on clinical, neuropsychological and neuroimaging criteria. The 4 groups were administered the Greek version of the Mini Mental State Examination (MMSE) [6] for the assessment of their general cognitive state. They were also administered detail personal and family history, however for elderly participants neurological, physiological, neuroimaging and neuropsychological examination was taken place. Children's parents after giving consensus for their assessment, were not attended the procedure.

The inclusion criteria for the children were regular school attendance and no mental, psychiatric or learning disabilities according to their medical history, teachers' and family report. They also had elementary knowledge of writing and reading. The exclusion criteria of all the participants were self-reported drug or alcohol abuse history, using cognition-affecting medication (except for drug therapy for the dementia disorder), or sensory deficits. Subjects with a history of head trauma, loss of consciousness, congestive heart failure, abnormal thyroid function, delirium, depression, epilepsy, psychosis, attention deficit disorder were also excluded after the administration of personal history. The mild demented-AD patients were in the first stages of the disease (CDR=1)[29] and their diagnosis based on clinical criteria laid down by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) [30]. All the participants were native non institutionalized Greek speakers, spoke Greek as first language and they didn't have financial or other benefit for their participation. The protocol for the research project conforms to the provisions of the Declaration of Helsinki (as revised in Tokyo 2004).

For the assessment of general cognitive status of children and elderly, as we referred, the examiners administered the Greek edition of the MMSE, a widely used screening test for the measurement of cognitive abilities and cognitive changes according to the time and the effects of potential therapeutic agents on cognitive abilities [31]. As it is wideworld clinical tool, we briefly refer that the MMSE assesses cognitive abilities as time and place orientation (maximum score:10), registration of 3 objects (maximum score:3), attention and calculation (serial 7s, spell 'world' backward) (maximum score:5), language abilities as naming, repetition, comprehension: 3 stage command, read and obey; sentence; copy design (maximum score:9) and recall (three words) (maximum score:3) [32]. The principal purpose of the test's construction was to screen mental impairment mainly in the elderly. However, it is used for children too [33, 8, 9, 6].

The MMSE performance is affected by age and education level [28] and the suggested cut-off is 24 points. More details about the MMSE disadvantages can be find in the literature [34-38]. Little is known whether the MMSE assesses the same abilities among people of different ages, though there are studies that reported correlations between the MMSE and other cognitive variables as executive functioning, memory, fluid intelligence, reading, speed, arithmetic, and spatial ability. The MMSE performance was associated with 3 cognitive constructs, naming vocabulary, reasoning and memory, but their respective contributions to the MMSE differed as a function of age and time [10].

Results

For the analysis of the results we used the Statistical Package for the Social Science (SPSS 20.0.0) and the Microsoft Windows 8.1. The mean of the general cognitive performance (MMSE score) according to the age (young and old children and elderly people) and the diagnosis (non demented, mild demented elderly) and the demographic characteristics of the participants are shown in table 1. Analytically, the scores of each item of the MMSE are presented in table 2. One way ANOVA indicated significant differences between groups in the general cognitive performance (MMSE) $F(3, 262)=76.42$, $p=.000$. Tukey analysis showed that only 2 subgroups, the last grades children and the non demented participants had no significant differences between them ($p>.05$) in the MMSE performance, though the first grades children showed significant better performance than the mild AD participants ($p=.000$, Mean Difference= 4.9). There was also significant differences between groups according to age and education level $F(3, 262)=5630.9$, $p=.000$, $F(3, 262)=106.42$ $p=.000$ respectively. As for the sex there were no significant differences between groups $x^2(1)=.388$ in the MMSE performance ($p>.050$). Our sample consisted of 132 male participants and 133 female. Table, 1 shows in more details the number of male and female participants according to the age and the cognitive status.

Table 2. Mean, S.D. of the 4 subgroups in the MMSE items.

MMSE items	Young Children		Old Children		Non Demented		Demented	
	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D
1. Day	0.98	0.11	0.92	0.26	1.00	0.00	0.39	0.49
2. Date	0.72	0.44	0.80	0.39	0.95	0.21	0.15	0.36
3. Month	0.93	0.24	1.0	0.00	1.00	0.00	0.63	0.48
4. Year	0.91	0.28	0.97	0.14	0.97	0.15	0.47	0.50
5. Season	0.93	0.24	0.96	0.17	1.00	0.00	0.92	0.27
Time Orientation (1-5)	4.50	0.71	4.6	0.55	4.9	0.25	2.5	1.3
6. Country	0.93	0.24	0.96	0.17	0.97	0.15	1.0	0.00
7. City	0.96	0.19	0.98	0.10	1.00	0.00	1.0	0.00
8. Roads	0.45	0.50	0.85	0.35	0.97	0.15	0.52	0.50
9. Floor	0.75	0.43	0.85	0.35	0.95	0.21	0.86	0.34
10. Room	0.96	0.19	1.00	0.00	1.00	0.00	1.0	0.00
Place Orientation (6-10)	4.00	0.86	4.6	0.59	4.9	0.36	4.4	0.64
11. Registration	2.9	0.38	3.00	0.00	2.98	0.15	2.97	0.16
12. Attention Serial 7s	3.11	1.98	4.21	1.16	4.48	0.93	2.92	2.00
13. Recall	2.48	0.94	2.75	0.55	2.16	0.97	0.23	0.48
14. Naming	2.00	0.00	1.9	0.10	1.9	0.15	1.9	0.22
15. Repetition	0.86	0.34	0.93	0.24	0.90	0.29	0.78	0.41
16. Read & obey	0.90	0.30	0.96	0.17	1.02	0.15	1.00	0.00
17. Copying	0.42	0.49	0.57	0.49	0.60	0.49	0.31	0.47
18. Writing	0.91	0.28	0.98	0.10	0.97	0.15	0.76	0.43
19. 3 stage command	2.80	0.43	2.83	0.44	2.81	0.39	2.18	0.86
Language (14-19)	7.9	0.30	8.17	0.25	8.20	0.27	6.93	0.39

According to the rate of the general cognitive state (MMSE) there was large effect size performance between young children and mild AD (Cohen's d=1.394) and young and old children (d= - 0.957). Non demented elderly scored much better than the mild AD according to the general cognitive state (MMSE scores) (p=.000, large effect size Cohen's d=2.505). Subsequently, we applied the MANOVA in order to investigate the 4 subgroups performance to the isolated MMSE items (e.g., orientation, language, registration, attention and recall). The orientation consisted of time and place options; the time orientation ability was assessed by the MMSE items of the day, date, month, year and season (5 points); the place orientation ability (5 points) was assessed by the naming of the country, city, addresses, hospital and the floor level. As general language performance (9 points) we considered the naming of 2 everyday visual objects (2 points), the writing of a phrase (1 point), the repetition (1 point), the 3 stage command (3 points), the read and obey (1 point), and the copy design (1 point). There were significant differences between the 4 subgroups to orientation $F(3, 262)=53.6$, p=.000, to attention $F(3, 262)=13.2$, p=.000, language $F(3, 262)=15.8$, p=.000 and recall $F(3, 262)=100.5$, p=.000 but not in registration (p>.05) (table, 3). More analytically, no statistically significant differences in performance were found to specific items as season, country, city, hospital, naming and repetition (p>.05) (table, 3).
participants to time orientation p=.000 (large effect size Cohen's d=1.909), language (p=.000, large effect size Cohen's d=2.787) and recall (p=.000, large effect size Cohen's d= 3.014), though they didn't score significantly better to place orientation and attention (p>.05). The old children showed significant better performance to recall (p=.000, mean difference=.58, medium effect size (Cohen's d=.0748) compared with that of the non demented elderly. They also showed better performance than the young children to place orientation (p=.000, large effect size, Cohen's d= 0.813) and attention, (p=.000, medium effect size, Cohen's d=0.677). Furthermore, the non demented participants performed significantly better than the young children to time and place orientation (p=.000) and attention (p=.000). Similarly, they scored much better than mild AD to time and place orientation (p=.000, large effect size Cohen's d= 2.563 for time, Cohen's d= 0.962 for place) attention (p=.000, large effect size Cohen's d= 1.000), language (p=.000, large effect size Cohen's d= 3.786) and recall (p=.000, large effect size Cohen's d= 2.521).

Subsequently, applying Tukey analysis we found that the young children performed better than the mild AD Applying factor analysis two components were loaded according to the childhood; for the young children the one component consisted of orientation and language score (.832, .835) and the second component consisted of the registration, the attention and recall ability (.781, .430, .743 respectively). For the old children we excluded the variable of registration which had zero variance, so factor analysis loaded 2 components; the 1st consisted of language (.636), attention (.522) and orientation (.589) and the 2nd of recall (.725). For the non demented elderly factor analysis loaded 3 components; the 1st consisted of orientation and language performance (.619, .861), the 2nd of attention (.906) and the 3rd of registration and recall (.867, .755). For the demented patients 3 components emerged too; the 1st consisted of orientation, language and registration (.748, .730, .780), the 2nd of attention (.948) and the 3rd of recall (.980).

Table 3. Comparing performance between 4 subgroups, df, F, p.

MMSE items	DF	F	P
1. Day	3	51.6	.000
2. Date	3	31.8	.000
3. Month	3	23.1	.000
4. Year	3	32.3	.000
5. Season	3	1.4	>.05
Time Orientation (1-5)	3	86.7	.000
6. Country	3	1.1	>.05
7. City	3	1.3	>.05
8. Addresses	3	23.0	.000
9. Floor	3	3.0	.027
10. Hospital	3	2.2	>.05
Place Orientation(6-10)	3	18.8	.000
11. Registration	3	1.5	>.05
12. Serial 7s	3	13.2	.000
13. Recall	3	100.5	.000
14. Naming	3	1.7	>.05
15. Repetition	3	2.3	>.05
16. Read & obey	3	3.9	.008
17. Copying	3	3.4	.016
18. Writing	3	7.1	.000
19. 3 stage commands	3	15.4	.000
Language(14-19)	3	15.8	.000

Discussion

Many researches, as we referred, clearly establish the existence of cross-sectional age-related declines for many cognitive functions and abilities prior to age 60 and even more after 70s in healthy educated adults [4]. The understanding of the range of cognitive development in children and cognitive decline in elderly has a significant impact for targeting effective interventions in neurocognitive disorders. This study aimed firstly to investigate the magnitude of cognitive development and decline in childhood and aging respectively through their performance in a brief and worldwide screening scale, the MMSE. Secondly, its aim was to compare the performance in some later acquired cognitive abilities (e.g., orientation, attention, language, recall) as they were expressed through the MMSE items in order to demonstrate the magnitude of cognitive development changes from 7 to 12 years old and cognitive decline from 60 to 87 years old using this knowledge for the successful management of aging.

According to the general cognitive performance from early to old childhood the MMSE score gradually increased 2.63 points during a period of about 2 years. This is considered as large effect size performance and it was expected between young and old children due to continuing maturation. Young children had also significant lower performance compared with that of the old children according to the later acquired abilities, as place orientation and attention-serial 7s, as a result of cognitive development and academic skills. The old children and the non demented elderly participants showed no significant differences in general cognitive performance except of the recall ability performance showing medium effect size better performance compared with that of the non demented elderly. This is a very important finding considering that from the one item 'registration' to the other 'delayed recall', only one item (the serial 7s) is inserted and the time which is running is not enough for the delayed recall as in other tests which is required at least 20 minutes to pass. So we might consider that if the required time for the delayed recall was more, then the effect size difference in performance perhaps would be bigger.

The young children performed much better in general cognitive performance compared to the mild AD participants (MEAN difference =4.96) showing a large effect size performance and poorer than both of the non demented and older children. Furthermore, they showed almost the same mean difference in the general cognitive performance compared with the old children (Mean difference= 2.63) and the non demented elderly (Mean difference= 2.61). These findings are in congruence with the development of cognitive abilities from early to old childhood and the subsequent cognitive decline in aging even administering brief screening test. Literature refers, as we discussed in the introduction that AD patients retrograde cognitively between the early grades of elementary school [8,6] and kindergarten [9], but in our research this happens even in mild AD. The cognitive decline in mAD patients seems to be more (mean difference 7.57) than the cognitive development in young children (mean difference 2.63). The question is if the MMSE measures the same cognitive abilities in children and elderly. Our results showed that it seems to measure the same abilities for both non demented and demented elderly as factor analysis showed high loadings to 3 components (recall, attention and language-orientation), though it seems to measure 2 components for young children; the one consisted of language and orientation and the 2nd consisted of registration, attention and recall. The loading of 2 components in young childhood, perhaps means that executive function and strategies for recall (delayed memory) are continued to be developed until adolescence as literature refers that developmental changes in executive functions are happened in the younger ages (8-11 years) and stabilization of performance in older age groups (12-17 years) [19]. For this reason perhaps attention and recall are loading one factor in young childhood, though in old childhood and elderly people are loading 2 different factors.

Our findings perhaps confirm also the "differentiation-dedifferentiation" hypothesis [20], which claims as we referred that cognitive abilities are undifferentiated during childhood, then go through differentiation at adulthood and again become undifferentiated in old age [21].

According to specific cognitive abilities assessed by the MMSE there were significant differences between the 4 subgroups to orientation, language, attention and recall. The 4 subgroups showed no significant differences performance to first acquired ability, registration which is acquired from very early childhood and maintained well even in moderate stages of dementia, as it does not presuppose high cognitive demands. Additionally the knowing of the name of the season, country, city and hospital (temporal and place orientation), the repetition of 3 words and naming of 2 very frequent, familiar and imageable objects (first acquired language abilities) seem to be retained well in both young children and mild AD indicating good place orientation for well-known places and naming ability for frequent everyday objects. This information is part of the overlearning knowledge, and most of this information is retained even in moderate dementia.

Assessing specific cognitive abilities measured by the MMSE for the 4 groups our results showed the following: *Orientation*: first grades children seemed to perform much better to time orientation compared with the mild ADs. However, they performed worse than the rest groups. Time orientation is seemed to be acquired well in old childhood though is impaired in mild AD. Time orientation, is supported mainly by everyday schooling in young and old children, though is diminished in mAD because of the poor functionality and the reduction of everyday activities. We tried to diminish the impact of schooling factor, as our research took place during vacation for the children and there was no schooling effect. Last grades children and non demented elderly didn't seem to have differences in the orientation items, perhaps because of their demanded daily living. The worse performance of young children according to the roads name perhaps means that they orientate themselves empirically without knowing names of addresses and/or are accompanied by their caregivers because of their young age.

Attention: first grades children showed similar performance compared with that of the mild ADs and poorer than that of the old children. This specific task (serial 7s) presupposes well integrated skills acquired gradually from the second to the fourth grade of the elementary school. Except of the academic skill, serial 7s presupposes working of the executive functioning that has been related to maturation of the circuitry of the prefrontal system, which continues through the second decade of life [39,1]. Attention and concentration abilities are continued to be improved compared to 4 to 6 years period [8]. Children may use executive-attentional resources even for basic counting [40]. Synaptic pruning begins around age 9 years and continues in the late teens, and myelination of the association areas continues through the second decade of life [1]. According to the literature attention processes mature around ages 10 to11 [41] or 12 years old [19] as our finding indicates too and seems to decline in mild AD. Mild AD patients perform worse in attention (serial 7s) than last grades children and non demented elderly, due to deterioration of both working memory ability and problem solving ability.

Recall (Delayed memory): it was expected that mild AD would show the poorest performance compared with that of first grades children and the other subgroups. It was also not surprising that young and old children had no significant difference in this task, as it was not a demanded one. Literature refers that older children recall more verbal items than younger children and 'memory capacity' increases with age for the additional reason that they use more often memory strategies and metamemory techniques than the younger one [42]. However, we didn't expect old children to score better than non demented elderly. Delayed recall is presupposed intact working memory, memory strategies, intact coding and restore processing. The better performance of older children than that of the non demented elderly, means perhaps that delayed recall begins to deteriorate even for simple tasks during normal aging and that is of the first abilities that impaired slightly, as other researches showed [3]. Further researches need in order to investigate the magnitude of this decline according to their life style, the content of the tasks and other demographic characteristics.

Language abilities: mild AD showed the poorest performance than the rest groups, even that of young children whose language abilities have not yet integrated. The MMSE can't detect language changes from young to old childhood but it seems to do this in pathological circumstances in elderly. Language tasks that assess simultaneously command comprehension and execution seem to have the poorest performance because of engagement of working memory, though confrontation naming tasks consisted of frequent everyday objects have the best performance.

Summarizing, our data indicate that there is large effect size difference in general cognitive abilities performance between first grades children and mild AD, as the literature refers. Additionally the first acquired abilities as registration and basic information for place orientation are maintained in mild AD patients and there is no difference between young children and mild ADs performance. Later acquired abilities as time orientation, attention, options of language abilities and recall are beginning to be impaired in mild AD patients and their performance is poorer than that in young children though their development is not well integrated yet. However, delayed recall performance of simple verbal matrix shows deterioration even in normal aging compared with that of older children showing a slight cognitive performance decline in normal aging, not necessary pathological. Our findings indicate that the next step is to investigate if the clinicians can apply the same level and context psychosocial interventions to mild AD participants and first grades children in above mentioned abilities, as they seem to show similar cognitive performance.

The restriction of this research was that we used a screening test and no batteries for assessing specific cognitive abilities, including tasks with different degrees of difficulty because of the lack of funding.

The authors declare that they have no conflicts of interest.

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Clinical developments in amyloid PET imaging

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Abstract

Given the fact that advancing age is the major risk factor for developing Alzheimer's disease (AD), the number of those afflicted is expected to increase along with world's population aging. One of the greater hindrances to establish effective treatment is the inability to have AD "on time", definetly diagnosed until autopsy. Even if current insights for neuroimaging combined with the elucidation of molecular processes in AD signl the ongoing development of new imaging tracers, "in vivo" visualisation of brain pathological changes by neuroimaging biomarkers do not yet offer clear advantages over current clinical diagnostic criteria for them to be accepted in everyday clinical practice. With the focus shifted to earlier diagnosis at a prodromal or better asymtopatic AD stge, recently introduced amyloid PET imaging techniques are proved to be important to define these stages.

Introduction

Alzheimer's disease (AD) is the most common type of dementia. Dementia can be defined as a clinical syndrome characterized by a cluster of symptoms and signs manifested by difficulties in memory, disturbances in language and other cognitive functions, changes in behaviors, and impairments in activities of daily living. Also leads to a loss of independent function that has a wide-ranging impact on individuals, families and healthcare systems [1]. Alzheimer's disease is a progressive neurodegenerative disorder and was named after the German psychiatrist Alois Alzheimer, who described this disorder more than one century ago, as the most common cause of dementia, accounting for up to 75% of all dementia cases.

Alzheimer's disease is the leading cause of dementia in old age. Because of its devastating impact on cognition and other behaviors and its chronic course, the disease poses enormous public health problems. Knowledge of disease prevalence is critical for public health planning and policy [2]. An estimated 5.2 million Americans of all ages had Alzheimer's disease in 2013. This includes an estimated 5 million people age 65 and older and approximately 200,000 individuals under age 65 who have younger-onset Alzheimer's. One in nine people age 65 and older (11%) has Alzheimer's disease. About one-third of people age 85 and older (32%) have Alzheimer's disease. Of those with Alzheimer's disease, an estimated 4% are under age 65, 13% are 65 to 74, 44% are 75 to 84, and 38 % are 85 or older [3,4]. The number of people surviving into their 80s, 90s and beyond is expected to grow dramatically due to advances in medicine and medical technology, as well as social and environmental conditions. Between 2010 and 2050, the oldest-old are expected to increase from 14 percent of all people age 65 and older in the United States to 20 percent of all people age 65 and older. This will result in an additional 13 million oldest-old people – individuals at the highest risk for developing Alzheimer's. The number of people in the United States with AD dementia will increase dramatically in the next 40 years unless preventive measures are developed [5].

Alzheimer's disease is a heterogeneous disorder with complex underlying neuropathology that is still not completely understood. The core component of the nervous system in the brain, is the neuron. A neuron is an electrically excitable cell that processes and transmits information by electro-chemical signaling. The average human brain has about 100 billion neurons and many more neuroglia which serve to support and protect the neurons. Each neuron may be connected to up to 10,000 other neurons, passing signals to each other via as many as 1,000 trillion synaptic connections. They allow signals to travel rapidly through the brain's circuits, creating the cellular basis of memories, thoughts, sensations, emotions, movements and skills. Alzheimer's disease interferes with the proper functioning of neurons and synapses. The two hallmark pathologies required for a diagnosis of Alzheimer's disease are the extracellular plaque deposits of the β-amyloid peptide and the flame-shaped neurofibrillary tangles of the microtubule binding protein tau [6]. In Alzheimer's disease, information transfer at synapses begins to fail, the number of synapses declines, and neurons eventually die. The accumulation of beta-amyloid is believed to interfere with the neuron-to-neuron communication at synapses and to contribute to cell death. An additional effect of beta-amyloid in the brain, which compounds the direct effects of beta-amyloid on neurons, is mediated by the stimulation of astroglia to become reactive. Once in the reactive state, glial cells deposit large amounts of growth-inhibitory molecules within the neuropil which could impair neuronal process survival and regeneration leading to neurite retraction and/or dystrophy around senile plaques in AD [7]. Tau tangles block the transport of nutrients and other essential molecules in the neuron and are also believed to contribute to cell death. The brains of people with advanced Alzheimer's show dramatic shrinkage from cell loss and widespread debris from dead and dying neurons.

The exact temporal relationship between the diverse structural alterations that follow is still a matter of active neuropathological and in vivo research. In the revised National Institute on Aging-Alzheimer's Association (NIA-AA) [8] neuropathological criteria, three different classification schemes have been adopted in parallel, depending on the phase of the spread of amyloid plaques) and neurofibrillary tangles and the amount of neuritic plaques as defined by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria.
The principal structural changes are:
• Loss of synaptic density, starting in the dentate gyrus and correlated to episodic memory scores
• Neuronal loss, starting in entorhinal cortex and correlated to cognitive scores
• Neurofibrillary tangles (NFT) and neuropil threads. Initially, neurofibrillary tangles are mainly present in entorhinal and perirhinal cortex spreading to the hippocampus (stage I/II). They subsequently spread to inferior temporal and lateral temporal cortex (stage III/IV) and then become widely distributed over neocortical association zones (stages V/VI). These NFT stages correlate relatively well with neuronal loss and with the severity of clinical symptoms.
• Aβ amyloid aggregates,which may take different forms: According to some authors, diffuse plaques should not be considered as pathological since they are not associated with synapse loss or neuronal loss, key features of Alzheimer's disease. Others have suggested that diffuse amyloid plaques are related to the presymptomatic stage of AD. In contrast to diffuse plaques, neuritic plaques stain with thioflavine S or Bielschowsky, indicative for the presence of tau pathology invading or surrounding the plaque. A time sequence analogous to that described for NFTs has been developed to describe the propagation of amyloid, starting in neocortical areas (phase 1) and then spreading to allocortical regions including, among other regions, entorhinal cortex, CA1, anterior and posterior cingulate (phase 2), basal forebrain nuclei, diencephalic nuclei and striatum (phase 3), brain stem nuclei (phase 4) and further into the molecular layer of the cerebellum (phase 5). At a certain stage the increase in β amyloid aggregates may level off, also referred to as a 'growth arrest' of the amyloid plaques [9].

The pathophysiological process of Alzheimer's disease is thought to begin many years before the diagnosis of AD dementia. In a recent prospective study on autosomal dominant Alzheimer's disease, Bateman et al. showed that as compared with noncarriers, mutation carriers tested by PIB-PET had significant fibrillar amyloid depositions in the precuneus 15 years before expected symptom onset [10]. Long "preclinical" phase of AD would provide a critical opportunity for therapeutic intervention; however, we need to further elucidate the link between the pathological cascade of AD and the emergence of clinical symptoms. The three stages of Alzheimer's disease proposed by the new criteria and guidelines are preclinical Alzheimer's disease, mild cognitive impairment (MCI) due to Alzheimer's disease, and dementia due to Alzheimer's disease. The 2011 criteria propose that Alzheimer's disease begins before the development of symptoms, and that new technologies have the potential to identify brain changes that precede the development of symptoms. Dementia due to Alzheimer's would encompass all stages of Alzheimer's disease commonly described today, from mild to moderate to severe [11]. Recent advances in neuroimaging, cerebrospinal fluid (CSF) assays, and other biomarkers now provide the ability to detect evidence of the AD pathophysiological process in vivo. Emerging data in clinically normal older individuals suggest that biomarker evidence of amyloid beta (Aβ) accumulation is associated with functional and structural brain alterations, consistent with the patterns of abnormality seen in patients with mild cognitive impairment (MCI) and AD dementia. Furthermore, clinical cohort studies suggest that there may be very subtle cognitive alterations that are detectable years before meeting criteria for MCI, and that predict progression to AD dementia. It is also clear, however, that some older individuals with the pathophysiological process of AD may not become symptomatic during their lifetime [12].

A multitude of diagnostic biomarkers and advanced imaging strategies have been developed to aid in the diagnosis and management of AD. The ability to characterize directly in humans the underlying pathophysiological processes is fundamental to progress in AD research and therapy. The new criteria and guidelines identify two biomarker categories: biomarkers showing the level of beta-amyloid accumulation in the brain and biomarkers showing that neurons in the brain are injured or actually degenerating. The most commonly used imaging modality in the study of AD has been volumetric T1-weighted magnetic resonance imaging (MRI). These images provide high-resolution (~1 mm) structural images with good tissue contrast. Longitudinal natural history cohort studies have demonstrated changes in global measures based on T1 images, such as whole brain volume or ventricular volume, as well as regional measures, particularly the hippocampus, that are several times higher in AD patients than in age-matched cognitively intact individuals. Most severe cortical thinning occurs in rostral medial temporal and anterior temporal cortex extending posteriorly along the middle temporalgyrus, inferior parietal cortex, temporoparietal junction (TPJ), ventral premotor cortex and the precuneus and posterior cingulate. Typically it has been shown greater effect sizes and therefore lower samples sizes for imaging when compared with clinical endpoints [13]. Research progress in Alzheimer's disease and molecular imaging over the past decade has made it possible to detect human brain amyloid-beta (Aβ) deposition during life using positron emission tomography (PET). Parallel progress has improved our understanding of Aβ as an important and therapeutically targetable component of AD pathology. While Aβ plaques are one of the defining pathologic features of AD, many otherwise normal elderly people have elevated levels of Aβ, as do patients with clinical syndromes other than AD dementia. The potential clinical utility of Aβ PET therefore requires careful consideration so that its role may be identified and placed in the proper clinical context [14].

To develop the new criteria, the Alzheimer's Association and SNMMI assembled an Amyloid Imaging Taskforce (AIT) consisting of dementia and imaging experts to review the scientific literature and develop consensus recommendations for the clinical use of this promising new technology. The AIT concluded that amyloid

imaging could potentially be helpful in the diagnosis of people with cognitive impairment when considered along with other clinical information, and when performed according to standardized protocols by trained staff. In addition, they emphasized that the decision whether or not to order amyloid imaging should be made only after a comprehensive evaluation by a physician experienced in the assessment and diagnosis of cognitive impairment and dementia, and only if the presence or absence of amyloid would increase certainty in the diagnosis and alter the treatment plan. According to the AIT amyloid imaging is appropriate in the situations listed below for individuals with all of the following characteristics: a cognitive complaint with objectively confirmed impairment, Alzheimer's disease as a possible diagnosis, but when the diagnosis is uncertain after a comprehensive evaluation by a dementia expert and when knowledge of the presence or absence of amyloid-beta pathology is expected to increase diagnostic certainty and alter management.

Amyloid imaging is appropriate in the situations listed below.

1. Patients with persistent or progressive unexplained mild cognitive impairment.
2. Patients satisfying core clinical criteria for possible Alzheimer's disease because of unclear clinical presentation, either atypical clinical course or etiologically mixed presentation
3. Patients with progressive dementia and atypically early age of onset (usually defined as 65 years or less in age).

Amyloid imaging is inappropriate in the situations listed below.

1. Patients with core clinical criteria for probable Alzheimer's disease with typical age of onset
2. To determine dementia severity
3. Solely based on a positive family history of dementia or presence of APOE4
4. Patients with a cognitive complaint that is unconfirmed on clinical examination
5. In lieu of genotyping for suspected autosomal mutation carriers
6. In asymptomatic individuals
7. Non-medical usage (e.g. legal, insurance coverage, or employment screening)

The first published attempt to image amyloid in vivo was reported by Friedland and colleagues, who administered a technetium-99 labeled anti-Aβ monoclonal antibody fragment to AD patients imaged with single photon emission computed tomography (SPECT). While this attempt was not successful, as the antibody proved too large to effectively cross the bloodbrain barrier, it instructed future attempts to develop amyloid imaging agents, focusing efforts on small molecules with increased brain permeability [15]. The first successful amyloid imaging agent employed in humans was 18fluoro-labelled1,1-dicyano-2-[6-(dimethylamino)-2-naphthalenyl]propene (FDDNP), a fluorinated derivative of a nonspecific cell membrane dye. FDDNP crosses the blood-brain barrier and determines the localization and load of senile plaques and neurofibrillary tangles in vivo in AD patients. The high-affinity binding of the probes to multiple binding sites on fibrils were consistent with results obtained with digital autoradiography, immunohistochemistry, and confocal fluorescence microscopy using human brain specimens of AD patients [16].

PET uses radiopharmaceuticals (radioactive drugs) to produce three-dimensional functional images of the brain or other body part. In amyloid PET imaging, the radiopharmaceutical is introduced into the body by injection into a vein and binds specifically to the amyloid protein, enabling visualization of areas in the brain where amyloid has clumped together into plaques. While a number of Aβ PET radiopharmaceuticals have been reported with human data, at present there are some that are in use at multiple sites to image Alzheimer pathology in vivo. Among these, [C-11]-(2-[4-methyl-amino phenyl]-1,3-benzothiazol-6-ol, or Pittsburgh Compound B (PiB) was the first to be described and is the most extensively studied [17]. Three ^{18}F-labelled tracers are being investigated in clinical trials; they have been developed as proprietary tracers for commercial distribution, which is possible because of the 110 min physical half-life of ^{18}F. Flutemetamol (GE-067) is the 3′-fluoro-derivative of PiB, whereas florbetaben (BAY-94-9172, AV-1) and florbetapir (AV-45) are stilbene and styrylpyridine derivatives, which exhibit high-affinity binding for fibrillary amyloid similar to PiB. These tracers are currently undergoing formal clinical trials to establish whether they can be used to accurately image fibrillary amyloid and to distinguish patients with AD from normal controls and those with other diseases that cause dementia. They might also be used as biomarkers to predict development of AD before onset of dementia and to assess the effect of anti-amyloid therapy. Negative amyloid scans indicate absence of AD with a high level of accuracy, but healthy elderly volunteers might have positive amyloid scans, so their predictive value in isolation is less clear [18].

Pittsburg compound B is a benzothiazole labeled with Carbon-11. Typically a dose of 250-450 MBq is injected while imaging time is about 40 to 90 minutes. The effective radiation dose for each patient is estimated between 1,3-2,4(5,3) mSv; μSv/MBq. PET imaging with amyloid tracers such as [11C] N-methyl [11C] 2-(4′methylaminophenyl)-6-hydroxy-benzothiazole (PIB) allows measurement of high cerebral amyloid-ß deposition in AD and thereby discriminating AD patients from healthy controls. High amyloid-ß load has also been demonstrated by PIB in patients with mild cognitive impairment (MCI) that later converts to AD. It has also been shown that PIB-PET may differentiate AD patients from patients with frontotemporal lobe dementia or Parkinson's disease whilst patients with dementia with Lewy bodies may show high but variable PIB retention [19]. PiB binds to insoluble fibrillary amyloid β with high affinity, but not to amorphous amyloid plaques and neurofibrillary tangles or other β sheets aggregates such as Lewy bodies [20]. Non-specific binding is seen mainly in white matter. Increased specific cortical binding has been reported in 90% or more patients with a clinical diagnosis of AD, whereas most healthy controls have cortical binding of less than 1,5-times that of the cerebellum, which usually serves as a reference structure [21]. 6-CN-PIB, a highly fluorescent derivative of 11C-PIB, has affinity for plaques, more so for neuritic than for diffuse plaques, as well as affinity for β amyloid in the vessel walls and for striatal plaques [22].

It is worth mentioning that there is significant overlap between the utility of amyloid imaging and measurement of CSF levels of amyloid-β1-42 (Aβ1-42), total-tau (t-tau), and phosphorylated tau (p-tau181p) as a screening tool (but not as a trial outcome measure). Both are primarily measures of brain Aβ pathology. Studies assessing concordance between these measures, have provided conflicting results [23]. While amyloid PET can quantify amyloid load throughout the brain, it is not clear what pool of brain Aβ42 is represented by changes in CSF Aβ42. The rich regional information in an amyloid PET scan also allows differentiation not only by quantitation but also regional specificity. This is especially important because it allows visual reads of amyloid PET scans to be highly accurate in distinguishing normal from abnormal scans. Visual reads are relatively easy to standardize because the technical variables in quantifying the amyloid PET signal are not a factor. Of course, visual reads would apply almost exclusively to use in screening and don't lend themselves to detection of small changes. Therefore, CSF Aβ42 and PiB PET may be equivalent screening measures for entry into clinical trials in AD dementia and MCI. Differences in the costs, practicalities and risks of the two procedures for the application at hand would determine which is better suited to a particular trial. CSF Aβ42 could have an advantage in identifying more amyloid-positive controls than PiB PET. Amyloid PET has the advantage of the easily standardizable visual read, but the greatest advantage of amyloid imaging for clinical trials is as a quantitative outcome measure for drugs expected to decrease fibrillar Aβ load [24].

Three ^{18}F-labelled tracers are being investigated in clinical trials; they have been developed as proprietary tracers for commercial distribution, which is possible because of the 110 min physical half-life of ^{18}F. Flutemetamol (GE-067) is the 3´-fl uoro-derivative of PiB, whereas florbetaben (BAY-94-9172, AV-1) and florbetapir (AV-45) are stilbene and styrylpyridine derivatives, which exhibit high-affinity binding for fibrillary amyloid similar to PiB they have high initial brain uptake, followed by wash-out of unbound tracer from cortical areas without fibrillary amyloid. Non-specific uptake in white matter is nearly twofold higher than with ^{11}C PiB. Most of the injected activity is cleared from the blood stream through the liver and gastrointestinal tract, and the rest is cleared through renal excretion.

Amyloid imaging with flutemetamol seems to be best performed about 90 min after tracer injection, when binding reaches a plateau relative to the cerebellar cortex. Similar to ^{11}C PiB, rapid systemic metabolism occurs resulting in production of mostly polar metabolites that are not expected to cross the blood-brain barrier and therefore would not interfere with brain imaging. Kinetic analysis of tracer binding showed reliable quantification by use of relative standardised uptake value ratios (SUVRs) with the cerebellar cortex as a reference region and data acquisition for this analysis requires only 20 min scanning and is feasible in a standard clinical setting. Sensitivity and specificity for discrimination between patients with AD and age-matched controls were both 93%. The mean cortical SUVR in patients was 2,2±0,4 versus 1,4±0,2 in controls. The association with quantitative uptake values of ^{11}C PIB was very high (r=0,9) in cortical areas, and test-retest variability was very small (1-4%). (18)F-Flutemetamol performs similarly to the (11) C-PIB parent molecule within the same subjects and provides high test-retest replicability and potentially much wider accessibility for clinical and research use [25]. Most commonly reported adverse reactions associated with flumetamol are: flushing (2%), increased blood pressure (1%), headache (1%), nausea (1%) and dizziness (1%) [26].

Images are typically obtained 60 min after injection of 185 MBq of fluorine-18 labelled styrylpyridine, florbetapir. After 30 min, more than half of plasma activity is associated with a demethylated and an acetylated derivative of florbetapir, both of which can cross the blood-brain barrier but do not bind to amyloid with high specificity. Preclinical studies indicated high binding affinity of florbetapir (18F) to Aβ fibrils and specific labeling of Aβ plaques in the cortical regions and hippocampus. In phase I and II clinical trials, florbetapir (18F) clearly differentiated patients with AD from healthy controls and uptake was most prominent in the precuneus. The neocortical-to-cerebellar tracer uptake ratio reached a plateau within 50 min post-injection. Results from a phase III clinical trial confirmed a strong correlation between florbetapir (18F) PET images and postmortem assessment of Aβ deposition. No serious adverse events were reported in any of the clinical trials of florbetapir (18F) [27]. Most commonly were reported: headache (2%), less than 1% develop musculoskeletal pain, fatigue, blood pressure increase and nausea. In an open-label, multicenter brain imaging study which was performed on 16 patients with AD and 16 cognitively healthy controls (HCs), the average cortical SUVR was 1,7±0,2 in patients with AD versus 1,3±0,2 in controls using either a parametric reference region method (DVR) or a simplified SUVR calculated from 10 min of scanning 50-60 min after (18)F-AV-45 administration [28].

Florbetaben is a fluorine-18 (18F)-labeled stilbene derivative that was developed as a positron emission tomography (PET) tracer for routine clinical application to visualize b-amyloid plaques in the Alzheimer's disease (AD) brain. The tracer successfully completed a global multicenter phase 0-III development program and was, as a consequence, recently approved by the US Food and Drug Administration and the European Medicines Agency. Florbetaben is an 18F-labeled polyethylene glycol stilbene derivative with high in vitro affinity and specificity for b-amyloid plaques. After intravenous bolus injection of 300 MBq florbetaben, an 18F-radioactivity concentration of 2-3 % injected dose/L was achieved in arterial plasma 10 min postinjection (p.i.). Brain radioactivity uptake was rapid, reaching a maximum of 6 % of injected 18F-radioactivity at 10 min p.i. Florbetaben was eliminated from the plasma of patients with AD dementia and healthy controls (HCs; primarily via the hepatobiliary system) with a mean biological half-life of 1 h. No relevant radioactivity was measured in blood at 4 h p.i..[29] It has the potential of predicting development of AD-related dementia in MCI cases and of assisting in the differential dementia diagnosis. Also, it has high diagnostic accuracy, as shown employing different gold standards (from clinical diagnosis to postmortem histopathology), for the detection of neuritic b-amyloid plaques in the brain. A negative florbetaben PET scan can reliably exclude AD [30]. Future developments in the field of b-amyloid PET imaging include the still

unsolved role of b-amyloid imaging in the progression to dementia, the presence of b-amyloid in healthy elderly individuals, and the use of (semi)-quantification in the assessment of b-amyloid load. In addition, there may also be a role for florbetaben within a combined PET/MRimaging setup. The effectiveness of new disease-modifying treatments may depend on the timely initiation of therapy before irreversible neuronal damage in slowly progressive neurodegenerative disorders. Integrated PET/MR imaging may be able to improve such early diagnosis through both structural and functional information [31]. Most commonly reported adverse reactions associated with florbetaben are: injection site pain (4%), injection site erythema (2%) and injection site irritations (1%).

Another ^{18}F-labelled amyloid tracer is 2-(1-(6-[(2-[^{18}F] fluoroethyl) (methyl)amino]-2-naphthyl)ethylidene) malononitrile (FDDNP), which binds to amyloid with less affinity and specificity than PiB and other related compounds. Increased binding in patients with AD and MCI has been reported, mainly in the hippocampus but also in brain areas with predominant amyloid deposits. Direct comparison of FDDNP with ^{11}C PiB showed differences in spatial distribution and more overlap between controls and patients than with ^{11}C PiB [32]. More selective tau tracers are in development, but the clinical usefulness of PET for imaging of tau is yet to be shown.

While considerable effort has focused on developing positron emission tomography β-amyloid imaging radiotracers for the early diagnosis of Alzheimer's disease, no radiotracer is available for the non-invasive quantification of tau. (18)F-THK523 does not bind to Aβ in vivo, while following the known distribution of paired helical filaments (PHF)-tau in the brain. While preclinical examination of THK523 has demonstrated its high affinity and selectivity for tau pathology both in vitro and in vivo, indicating that (18)F-THK523 fulfils ligand criteria for human imaging trials [33]. Significantly higher cortical (18)F-THK523 retention in AD patients as well as the association of hippocampal (18)F-THK523 retention with cognitive parameters and hippocampal volume suggests (18)F-THK523 selectively binds to tau in AD patients. Unfortunately, the very high (18)F-THK523 retention in white matter precludes simple visual inspection of the images, preventing its use in research or clinical settings [34].

Although the Alzheimer's Association, SNMMI, and the Amyloid Imaging Taskforce supports Medicare coverage of amyloid imaging in limited populations as defined by the Amyloid Imaging Taskforce appropriate use criteria, Medicare does not cover it except for use in Coverage with Evidence Development (CED) programs, which are clinical trials that assess how amyloid imaging improves patient outcomes or advances patient treatment options. Commercial insurance coverage varies. Out-of-pocket costs for PET scans average $3,000 per test or greater.

Amyloid imaging provides a direct window on one of the components of AD. This component stands in a relatively complex relationship to a diversity of other component processes. Only some of these processes can be imaged and there is an ongoing search for techniques to detect and quantify in vivo some of the other pathogenetic mechanisms, such as glial cell involvement or tau hyperphosphorylation Amyloid imaging provides hope for progress as it allows for direct measurement of one component contributing to AD-related cognitive decline. This can enhance the chance of success of trials by allowing to restrict inclusion to those patients who have the target of interest and by showing whether the drug engages the target or not. While amyloid imaging is already being introduced to the market, many gaps can be identified in our evidence-basedmedical knowledge of its role in clinical practice. These gaps will have to be filled over the years to come by studies of clinical utility and added value.

The authors declare that they have no conflicts of interest.

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Correlating cognitive status with electrophysiological brain networks: an exploratory study in patients with Multiple Sclerosis

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Abstract

Objective: The investigation of brain connectivity in Multiple Sclerosis (MS) from multi-channel EEG, MEG or fMRI has attracted research interest in recent years. This line of research is suitable for the investigation of cognitive dysfunction that is regarded as a common and debilitating feature of this disease. Brain connectivity approaches are particularly appropriate for investigating this critical disease aspect. **Subjects and Methods**: Ten patients fulfilling the Poser's clinical criteria for definite MS entered the study after giving informed consent for the procedures which were approved by an institutional ethics committee and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Exclusion criteria include severe cognitive decline and inability to understand and sign the informed consent or comply with the experimental procedures. hd-EEG was performed in electrically shielded conditions using a 64-channel hd-EEG device (TMS-compatible eXimia, Nexstim Oy,Finland). Brain networks were constructed in artifact free epochs during resting state using linear and non-linear measures of brain connectivity. Study participants were tested with a battery of neuropsychological tests assessing the following cognitive domains: information processing speed, psychomotor functioning, attention, verbal memory, working memory, executive functioning and visuospatial memory. Individual subjects' scores were converted to z-scores the average of which provided an overall cognitive score. Thereafter, the composite neuropsychological performance as well as individual cognitive domain scores were correlated with electrophysiological brain network parameters. **Conclusion:** Brain networks constructed using hd-EEG and brain connectivity measures are a promising technique for investigating and monitoring cognitive status in patients with Multiple Sclerosis.

Introduction

Multiple Sclerosis (MS) is one of the commonest serious neurological disorders affecting more than 2,500,000 people worldwide [1]. It stands out among Central Nervous System (CNS) diseases by virtue of its frequency, chronicity and tendency to attack young adults representing the primary cause of neurological disability during the earlier part of adulthood. The pathological hallmark of MS is the presence of multiple CNS lesions, known as plaques, which are characterized by various degrees of inflammation, demyelination and gliosis. In addition, axonal loss, which may reflect neurodegenerative mechanisms [2], has been recently appreciated as an important disease component [3].

The clinical manifestations of MS are protean and comprise motor, visual, sensory, autonomic and cerebellar symptoms and signs as well as cognitive decline and psychiatric co-morbidities. Impairment of cognitive function occurs in 40-65% of MS patients [4] and involves primarily the areas of complex attention, information processing speed, episodic memory and executive functions. Both white and grey matter damage are implicated in the development of cognitive impairment with white matter damage representing the most accurate predictor of long-term cognitive deficits [5]. Cognitive impairment in MS has been intensively investigated using neuropsychological, neuroradiological and, to a lesser extent, electrophysiological techniques [6]. These studies identified subtle cognitive changes even at the early disease stages and ascribed cognitive deficits to a disruption of connecting intercortical and subcortical pathways [7] suggesting that cognitive impairment in MS can be conceptualized as a form of "disconnection" syndrome.

EEG-based neurophysiological approaches are well-suited for exploring brain connectivity in health and disease due to their millisecond temporal resolution. Leocani et al. [7], investigated EEG coherence, which is the most widely used measure of interaction between brain areas, in patients with clinically definite MS and reported decreased coherence values in discrete bands compared to healthy subjects. This pioneering study provided important insight into the pathophysiological substrate of cognitive impairment in MS. On the other hand, there are certain methodological issues related to the interpretation of coherence estimates in brain connectivity studies. In scalp-recorded EEG data, the most important issue relates to the phenomenon of volume conduction which results in mixing of cortical source activities at the sensor level and the generation of spurious correlations that do not reflect real patterns of brain connectivity. Another issue is the effect of particular references which may act as significant confounders in the estimation of coherence. Recently, solutions to these important theoretical issues emerged. For instance, [8] described the imaginary part of coherence (icoh), which removes efficiently the spurious coherence caused by volume conduction in EEG sensor-space analysis. In addition, Qin et al [9] described the reference to infinity (REST) which purportedly minimizes the distortion produced by active reference schemes. However, these theoretical advances have not been implemented in the analysis of EEG data of MS patients so far.

The present exploratory methodological study was designed to: a) investigate the imaginary part of coherence as a brain connectivity measure in patients with MS and b) elucidate the effect of various EEG reference schemes, including the recently proposed reference to infinity. Essentially, it is a pilot study aiming to optimize the assessment of brain connectivity tools for the investigation of cognitive impairment in MS.

Subjects and methods

Study participants gave informed consent for the procedures, which were approved by an institutional review board and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. We included 10 patients with clinically definite MS according to the Poser's criteria (8 women, median age 32 years, range 22-53) and an age-matched group of 11 healthy controls (6 women, median age 26 years, range 19-47). Exclusion criteria included severe cognitive decline, use of centrally active drugs (save for immunomodulatory treatments), contra-indications to Transcranial Magnetic Stimulation (TMS) and inability to understand and sign the informed consent or comply with the experimental procedures.

EEG recordings combined with TMS (TMS-EEG) were performed according to recent methodological guidelines [10] in an electrically shielded room. EEG was recorded with a 64-channel high density, TMS-compatible EEG device (eXimia, Nexstim Ltd., Helsinki, Finland). In order to minimize the TMS-induced artifact, the minipuncture technique of Julkunen et al was employed [11]. Briefly, after preparing electrode contacts by rubbing the skin using a wooden stick, the epithelium under the electrode contacts was electrically short-circuited by delivering four punctures per electrode with a custom-made mini-puncturing instrument. During TMS sessions, EEG was recorded continuously with sixty Ag/AgCl pellet electrodes, specially designed so as to avoid overheating by TMS-induced eddy currents and connected to a TMS-compatible EEG amplifier (eXimia, Nexstim Ltd., Helsinki, Finland). EOG was measured simultaneously. During acquisition, the reference channel was attached to the right mastoid and the ground electrode was placed on the right zygomatic bone at a distance of approximately 4 cm from each other. The EEG signals were band-pass filtered from 0.1 to 500 Hz and sampled with a 1450 Hz sampling frequency and 16-bit precision.

For each patient, a 5 minute continuous relaxed, resting state EEG was recorded with eyes opened every 30 sec followed by 5 minutes resting state EEG with eyes closed and TMS stimuli delivered every 15 seconds. Vigilance levels remained stable during the recordings in all subjects. For the present analysis, we extracted an EEG epoch of approximately 1.4 s prior to the time of TMS administration, containing 283 data points (the exact time is 1.415 s corresponding to an initially selected segment of 2048 data points and then down-sampled from 1450 Hz to 200 Hz). For each subject a mean of 15 artifact-free EEG epochs were analyzed. The details of brain stimulation are not relevant to the main objectives of the present article, which focuses on the pre-stimulation period, and will not be currently discussed.

Data analysis

After TMS-induced artifact removal [12], we applied a band-pass filter (low pass frequency 0.01 Hz and high pass frequency 100 Hz, fillter order 60) and down-sampled to 200 Hz. The EEG data were then re-referenced to common average (ComAve) as well as to infinity (REST). These references together with the right mastoid (Mastoid), employed during acquisition, constituted the three main categories of analysis [9].

For the estimation of the imaginary part of coherence we adopted the following approach. Let us assume that we have a set of simultaneous EEG signals $x_1(t)...x_K(t)$. We first apply the regression of vector autoregressive model of order p, VAR(p) on the multivariate time series. Hence each time series $x_j(t)$ is decomposed as:

$$X_{j,t} = a_{j1,1}X_{1,t-1} + \cdots + a_{j1,p}X_{1,t-p} + \cdots + a_{ji,1}X_{i,t-1} + \cdots + a_{ji,p}X_{i,t-p}$$
$$\ldots + a_{jK,1}X_{K,t-1} + \cdots + a_{jK,p}X_{K,t-p} + u_{j,t} \quad u_{j,t}\text{: white noise}$$

Consequently we perform a Fourier transformation to the coefficients of the model:

$$A_{ji}(f) = \begin{cases} 1 - \sum_{r=1}^{p} a_{ji}(r)e^{-i2\pi fr}, & if\ i = j \\ -\sum_{r=1}^{p} a_{ji}(r)e^{-i2\pi fr}, & otherwise \end{cases}$$

We then compute the transfer function $H(f) = A^{-1}(f)$ and the cross -spectral matrix $S(f)=H(f)\Sigma H^H(f)$, where Σ is the covariance matrix of all time series$x_1(t)...x_K(t)$ and H^H is the Hermitian transpose of H. S is a matrix of size KxK. Coherency is defined as:

$$C_{ij}(f) \equiv \frac{S_{ij}(f)}{(S_{ii}(f)S_{jj}(f))^{1/2}}$$

which is a complex number. The imaginary part of this complex number represents imaginary coherency (icoh). After the computation of this measure for all the predefined frequencies f, we may focus on a certain energy band by simply computing the average over the frequencies of this band.

Statistical analysis was performed using SPSS 20 (SPSS Inc.) Interactions between the factors Group (healthy subjects versus MS patients), Reference scheme (Mastoid, Common Average, REST) and Frequency band (δ,θ,α,β,γ) were explored with a three-way analysis of variance and corrected for multiple comparisons with a Benjamini-Hochberg post-test. For all tests, $p<0.05$ was the level of significance.

Neuropsychological evaluation

All participants were administered Digit span Forward and Backward (DS), Logical Memory I & II (LM) tasks of Wechsler Memory Scale-III, Symbol Digit Modalities Test (SDMT), Stroop Color-Word Test (SCWT), Verbal Fluency Test (VFT), Trail Making Test (TMT) and Rey Complex Figure Test (RCFT). Patients' scores were converted to z-scores, using the mean and standard deviations of the healthy group for each variable, separately. This calculation allows to quickly compare patients' performance to controls' scores. In accordance with [13], seven cognitive indexes were formed as follows: information processing speed (SDMT), psychomotor functioning (TMT), attention (SCWT), verbal memory (LM), working memory (DS), executive functions (VFT), and visuospatial memory (RCFT). Furthermore, a total cognition index score was calculated by averaging z-scores from the aforementioned seven cognitive indexes.

Results

All subjects completed the experimental sessions and did not report any untoward side effects. The estimated values of imaginary coherence in patients and controls for five frequency bands (delta (δ), theta (θ), alpha (α), beta (β), & gamma (γ)) in relation to the three employed reference schemes (Mastoid, Common Average, REST) are summarized in Tables 1-3 (as means ± SEM) and are graphically depicted in Figure 1.

In both patients and healthy controls, the Mastoid reference resulted in significantly lower icoh values compared to Common Average and REST ($p<0.001$) whereas the latter two references were not significantly different ($p>0.05$) (Table 3). This finding was consistent across all frequency bands (Fig 1). It should be noted that icoh values differed significantly in a frequency-specific manner ($p<0.001$) (Table 2).

The values of icoh did not differ significantly between patients and controls (Table 1) although a trend was observed ($p=0.07$). Finally, the values of imaginary coherence were not correlated with the results of the psychometric tests ($p>0.05$).

Table 1. Imaginary coherence values in MS patients and healthy controls

	icoh	SEM
Healthy subjects	,11245	,00103
MS patients	,11425	,001580

Table 2. Imaginary coherence values in MS patients and healthy controls (for the five frequency bands)

Bands	icoh	SEM
Delta	,08680	,0013
Theta	,14524	,00206
Alpha	,16034	,00188
Beta	,10228	,00153
Gamma	,00702	,00083

Table 3. Imaginary coherence values in MS patients and healthy controls (for the three reference schemes)

Reference	icoh	SEM
Mastoid	,0061	,0009
Common Average	,14001	,00128
REST	,13789	,00133

Table 4. Seven cognitive indexes and Total Cognitive Index scores are presented for MS patients and the healthy controls.

Cognitive Index	Healthy Controls (n=9)	MS patients (n=5)
Psychomotor Functioning	-0.000(0.845)	0.629 (0.964)
Attention	-0.000(0.677)	-5.252(1.968)
Information Processing Speed	0.000(1.000)	-3.672(1.987)
Verbal Memory	0.000(0.974)	-2.937(1.283)
Working Memory	-.000(0.910)	-2.430(1.279)
Executive Functions	.000(.746)	-1.429(0.797)
Visual-Spatial Memory	.000(0.956)	-1.586(0.804)
Total Cognitive Index	.000(0.394)	-2.382(0.618)

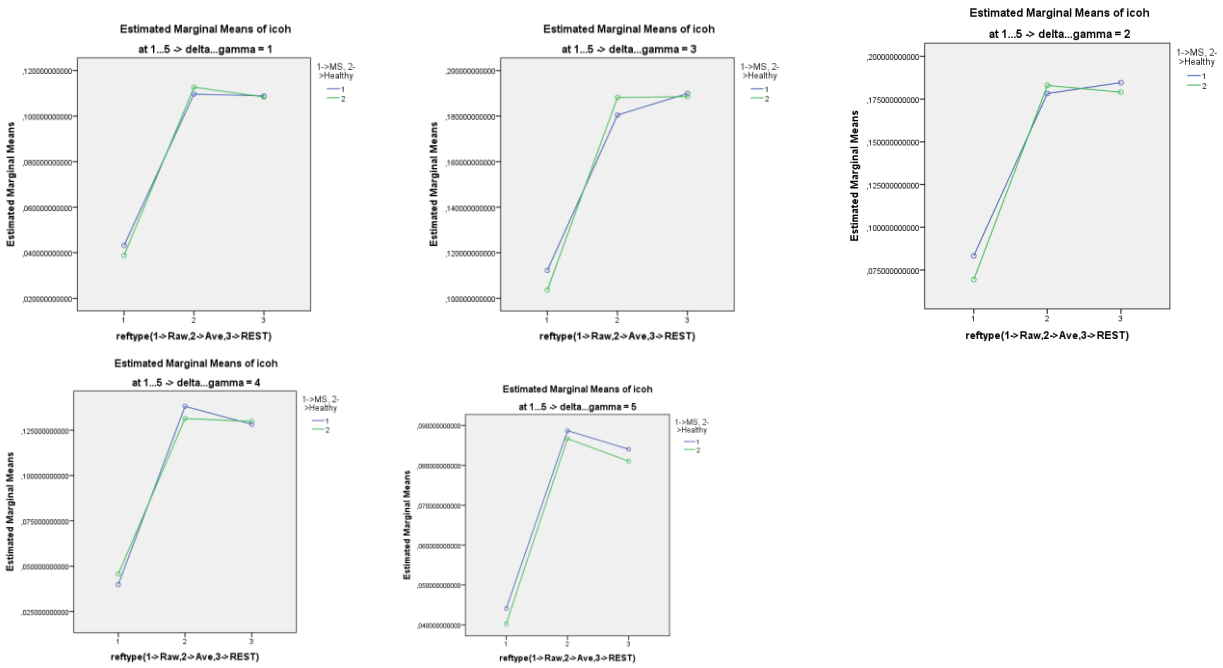

Figure 1. Graphical presentation of estimated mean values of imaginary coherence (ich) in patients and controls for five frequency bands (delta (δ), theta (θ), alpha (α), beta (β), & gamma (γ)) in relation to the three employed reference schemes (Mastoid, Common Average, REST)

Neuropsychological testing

Results are presented in Table 4.

Scores greater than 2 Standard Deviations are considered to reflect cognitive dysfunction. It was found that MS patients scored below 2 S.D in working memory, verbal memory, information processing speed and attention indexes. Their overall cognitive functioning, as reflected by the total cognitive index, was also found to be impaired. On the other hand, scores in psychomotor functioning, executive functions and visual-spatial memory indexes were not found to exceed 2 S.D, thus performance in these cognitive domains were not considered to be significantly affected.

Discussion

The present exploratory study investigated in a pilot sample of MS patients and healthy controls, the imaginary part of coherence, which is a recently introduced measure of brain connectivity, and addressed the importance of the employed reference scheme in this type of analysis. It is concluded that the reference type affects significantly the estimated values of imaginary coherence and therefore should be carefully selected in the context of similar studies.

The impetus for designing this study was provided by the fact that previous EEG investigations in the field of MS [6] relied on Coherence, which is widely used as a simple measure of brain connectivity but is characterized from certain inherent shortcomings [14]. For instance, coherence confounds amplitude and phase correlations and is sensitive to volume conduction effects, the latter being a critical factor in scalp EEG studies. The phenomenon of volume conduction has been long recognized as a significant confounder in the analysis of EEG data and is ascribed to the mixing of signals from various sources before their registration at the sensor space. As an end-result of this phenomenon, the activity of a single source can be registered at numerous EEG sensors simultaneously creating the false impression of apparent connectivity between essentially unconnected sensors (and sources by extension). One of the methods for overcoming this intractable problem uses the imaginary part of coherency [8] which theoretically is insensitive to volume conduction effects and therefore is superior to the real coherency component as a method for investigating brain interactions.

In our pilot study, the estimated values of the imaginary part of coherence did not differ significantly between MS patients and controls. There are various possible explanations for this negative result in addition to the small sample size of this essentially exploratory study. For instance, it is worth noting that the experimental paradigm employed in the present study was passive which may be a suboptimal design for differentiating patients from controls. Task-related parameters, such as the difficulty of the task, are critical determinants of the sensitivity of cognitive electrophysiological studies [15]. It is conceivable that an active paradigm (for instance, involving the activation of a Working Memory network during EEG acquisition) or the perturbation of brain networks with parametrizable, external stimuli (i.e. TMS stimuli) may enhance the sensitivity of the methods. These approaches are currently under study.

In contrast to the non-significant group effect, the reference type influenced significantly the results of our connectivity analysis. The importance of selecting an appropriate reference in connectivity studies has been previously emphasized. For instance, Fein et al [16] & Guevara et al, [17] suggest that a common average reference will result in erroneous estimation of coherence values particularly in cases with a low electrode number and coverage exclusively of the upper hemisphere of the head. On the other hand, increased activity at an active reference electrode may lead to falsely increased coherence values [18]. Qin et al, [9] addressed the issue of reference choice in the investigation of the default

mode network constructed by EEG coherence and power data and concluded that the reference at infinity (REST) compared favorably to other commonly used reference schemes (including left mastoid, linked mastoids and average reference). Importantly, in a simulated set of EEG data, REST was found to be associated with a minimal residual error of coherence whereas other references resulted in significantly higher error values. In our study, the use of different references resulted in different patterns of brain connectivity, with mastoid reference producing the lower estimates of imaginary coherence whereas common average and REST yielded similar results.

In conclusion, our results indicate that methodological factors (i.e. the choice of an appropriate reference scheme, a robust connectivity measure and a proper experimental paradigm) are of crucial importance for the construction of EEG-based brain networks for the investigation and monitoring of cognitive status in MS patients.

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Web services for Greek informal carers

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Abstract

The INNOVAGE project is dedicated to developing, surveying and cataloguing, social innovations for older people. Four new innovations will be developed and tested: a) social innovation for user – driven housing of older people, b) a web-platform for informal carers of older people, c) social intervention for improving obesity in old age, d) social innovation for activation of people with dementia living in long term care institutions. Italian National Institute of Health and Science on Aging (INRCA) (www.inrca.it) and Eurocarers Association (www.eurocarers.org) are the partners responsible for developing and implementing a multilingual web platform for informal carers in 27 EU Member States. An innovAge carers associations network has been established based on the Eurocarers organisations network. National organizations, members of INNOVAGE network, are responsible for developing national information and disseminating the web platform at national level. Athens Association of Alzheimer's Disease and Related Disorders is an official member of the INNOVAGE network and participates in the development of the Greek version of the INNOVAGE web platform. The platform will provide to end-users services such as: national information on care and support services, legal and financial information, information about the most common impairments of older people, strategies and information about coping with caregiving. Interactive services, social network, forum, chat, video conferencing tools will be also available. The Greek version of the web platform will be available in May 2015.

Introduction

The support services for family carers vary considerably throughout Europe, being virtually non-existent in several countries and piecemeal and fragmented in a number of others. The EUROFAMCARE Pan European Background Report, based on 23 national reports, suggested the existence of three main models of support [1,2]: 1) Scandinavian model – typified by Sweden, where the emphasis has traditionally been on supporting the older person and dedicated services for family carers are beginning to emerge, 2) Southern European or family model – typified by Greece, where the primary responsibility for supporting older people rests with the family and where public services to support family carers are limited or non-existent, unless in cases of extreme economic hardship or the absence of family, 3) a smaller group of countries – where carers are recognized as citizens with specific rights. These include the UK, Ireland and Netherlands.

Family carers remain "invisible and undervalued" in many countries, even though the unpaid caregiving contributes to the state in economic aspect. The caregiving affects carers' well being and quality of life, their health and socio-economic status and for those reasons the state has to develop supporting services for unpaid caregivers [1,2].

The carers in Europe and Greece

A carer can provide more than one aspect of care. Most often the term refers to a family member or friend who aids the older person - usually refers to informal, unpaid assistance for the physical and emotional needs of another person. Family members or friends frequently provide this type of care [3]. An informal carer has been defined by Eurocarers as "a carer that looks after family, partners, friends or neighbors in need of help because they are ill, frail or have a disability. The care they provide is unpaid"[4].

In all countries, women are more likely to be carers and are also more likely to provide more physically intimate, emotionally demanding and longer term care [5]. The majority of people who have reported involvement in the care of an older person at least once or twice per week belong to the 50-64 age group (20%), followed by the 35-49 age group (17%) [6].The vast majority of women in the middle years of life may try to conciliate work and care [7].

According to the Eurofamcare results [1,2] the mean age of Greek family carers was 51,7 years though the actual range of carer ages was from 18-95 years. This made them slightly younger than family carers in other countries. Women were overwhelmingly the main providers of care, representing 80,9% to family carers and these findings are similar to the findings for other countries. In Greece 47,2% were still working for meanly 40 hours with a maximum of 140 hours a week. The findings showed that the family carers of a dependent person shared the same household in 50,7% of the sample. The mean number of hours of caring to the main dependent cared for person was 51 hours per week. Finally the majority of family carers (80,9%) cared for just one dependent older person,

16,8% were caring for 2 older dependent persons, while 2,3% were caring for 3 or more dependent older people.

Caring experience

The caring experience is a complex phenomenon and can dramatically impact on all aspects of the family members. Caring negatively affects the physical, psychological, emotional, social and financial status of the caregivers, commonly described as "carers burden" [8].

Caring is associated with changes in physical health status through multiple pathways. Carers report poorer levels of health, a great number of physical symptoms and more chronic illnesses. Carers are most likely to experience depression and stress due to their caring role and sometime feel unappreciated and neglected by others. They may also have to limit the time and energy they invest in relationships or in their jobs. The caring role leads to social isolation and provokes difficulties in occupational responsibilities [9-11].

Support services for carers in Greece

Support services for carers in Greece are mainly provided by non profit associations and specifically, condition specific associations. These services are supervised by the Ministry of Health and have been mainly developed under the Psychorgos Program for Mental Health Reform [12].

In recent years, web based support services for carers have attracted the attention of health professionals and researchers in Greece and are mainly developed and provided through European funded projects. In many cases the service provision is finalized together with the lifecycle of the project.

innovAge web platform

Different kinds of interventions supporting informal carers have been developed and assessed, especially in terms of psycho-educational or therapeutic sessions with professionals. Services delivered through the internet seem to constitute the first step for reaching and making available essential services to carers in Europe.

The aim of this paper is to present the development of the new multilingual web platform **InformCare**, supporting informal carers of older people in 27 EU Member States, including Greece, as part of the INNOVAGE project, funded by FP7. Additionally, a limited number of web services have been developed for secondary target groups: care professionals and employers of carers in paid employment. The overall goal of the new web platform is to improve the quality of life of informal carers through the provision of web-based support services. This paper summarises the main steps and methodology used for the development phase, as well as concerning the pilot test and implementation of the platform, which should be publicly available in May 2015.The Italian National Institute of Health and Science on Aging (INRCA) and Eurocarers are the partners involved to carry out these activities.

Characteristics of the web platform

The development of the web platform was based to a user-centred design approach. Carers' needs and types of support were defined through previous experience of relevant European research projects such as EUROFAMCARE, Carers@Work and CARICT [13-15].

A review of good practices was then conducted by analyzing available web-based services for informal carers, care professionals and employers of working carers across Europe [16-17].

Furthermore, a consultation process with external experts, users and stakeholders was organized: overall, 58 people replied to on-line surveys. The aim was to gain opinions on seven core dimensions:

- Relevance of user's need: the importance of carers' needs (and related types of support) according to carers;
- Implementability of services: to what extent a user need can be addressed by a web-based service;
- Digital competences of users: the ability of end users to use different types of web tools;
- Appropriateness of web tools: the identification of the most appropriate web tools for meeting carers' needs;
- User-friendliness: the assessment of which web tools could be much more user-friendly for target groups;
- Sustainability: the estimation of efforts and resources needed by carers organisations to sustain a web platform with selected services and contents;
- Feasibility: based on technical requirements, how feasible would it be to develop and continue implementing selected web tools.

Piloting Phase

The second project phase concerned a pilot study carried out in November 2013 - August 2014 for testing the web-based support services and for collecting first evidence of their usability and effectiveness. The pilot was a one-group pretest-posttest study. Services have been piloted in Italy, Germany and Sweden, for a period of 12 weeks and 120 users have tested the services. Questionnaires have been administered to carers and different dimensions related to the carer have been assessed:

- Demographic, socio-economic status and background characteristics;
- Health status;
- Quality of life;
- Self-perception of carer's role;
- Perceived social support;
- Usability of the web services;
- Perceived usefulness and appropriateness of the services;

- Navigation patterns of the carer through the platform.

An expert meeting with external researchers and stakeholders has been organized at the end of the assessment, in order to discuss and validate results from the pilot test.

Online services provided

The following set of services has been selected to be included in the platform:

- Information of most frequent conditions of older people: Dementia, Parkinson's Disease, Stroke, Arthritis
- Available carer support services in national level
- Carers' needs and available information and services assisting carers to manage their burden
- Financial and legal information in national level
- Additionally a set of interactive services have been selected:
    - Individual support via e-mail
    - video-conferencing sessions
    - forum
    - social network

Each country had the flexibility to select the set of services that would be able to sustain. In Greece, the interactive services selected are: messages, video-conferencing tools and social network

Conclusions

The development and implementation of this new platform will constitute a first step for filling the gap that still occurs in many European contexts and for fostering recognition of carers at all levels. In Greece, services are provided to carers mainly by non profit organisations. At the moment no active carers organization has been established yet, even if some small scale efforts have been started. The role of Greek carers remains unrecognized by the state. The development of online services for carers as part of a wider project, including strategies and services provided to other countries for carers could increase opportunities of self-empowering and assist in creating strong user organisations with advocacy and lobbying for carers rights!

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An e-learning tool for the paid caregivers in Greece

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Abstract

It is estimated that 80% of people with dementia in Greece remain at home and receive informal care. The care providers are often migrant women with low education level without training in health care issues**. Aim:**The aim of this study is to transfer an innovative training program, SET CARE to Greece and Bulgaria from the Italian program "ASPASIA" that could meetthe needs of care workers.The didactic units focus on themes such as: basic healthcare skills, basic assistance skills, relationship and communication with the elderly, rights and duties of the care worker, national health and service systems, strategies to deal with older people with Dementia; computer skills **Method:**In total 31 people participated in the piloting phase in Greece and Bulgaria aiming to assess the quality of the SET CARE e-learning tool. **Results:** The results are in accordance with the findings of the Italian research, where the ASPASIA project is implemented and widely accepted from careworkers. **Discussion:** The majority of the sample insists that there is great need for a training program relating to caring issues and also it is very important for the careworkers to learn the Greek Language in order to assist the older people.

Introduction

The ageing population in Greece has increased in last decades and constitutes the 19% of the general population. As a result,an increasing proportion of older people aremost likely to suffer serious health problems that render them unable to care forthemselves and live on their own.Additionally it is estimated that 200.000 people suffer from dementia and need qualified assistance. The majority of people with dementia in the final stage of the disease remains at home and being cared from family members and paid carer [1].In most cases Greek family undertakes exclusively the care responsibilities of their loved one and only a small percentage sharescaregiving tasks with a paid carer[2]. In Greece 20% of the paid carers are immigrants (percentage that refer only to legal immigrants) and 2/3 of them come from the ex-Soviet Union and Bulgaria [3].

There is lack of evidence on quantitative and qualitative data for migration in Greece. The National Statistical Service of Greece (ESYE), the Ministry of Labour, the Ministry of Education and Religious Affairs, the Ministry of Foreign Affairs, the Ministry of Public Order, the Ministry of Internal Affairs and the Institution mainly provide data for Social Security (IKA). The first nationwidedata collection had derived from the first regularization programme of 1998.The most recent source of information is the 2004/5 HouseholdBudget Survey (HBS) carried out by ESYE [3].According to this report the majority of immigrants are migrating from neighboring Balkan countries, such as Albania and Bulgaria. Immigrants from Albania are estimated to be more than half of all immigrants (57.5%) and the second largest group is from Bulgaria (4.6%), followed by immigrants from Georgia (3.0%), Romania (2.9%), and Russia (2.3%) [4]. According to statistical data concerning the educational level of immigrant women, 2% are illiterate, 38% have primary education, 51% secondary, and 9% have a higher education [5]. Robolis [6] mentions that 13% of employees in Greece are immigrant and 75% of them are employed in domestic labor (taking care of children or elderly persons, house cleaning, etc.) [3]. Women immigrants are usually not occupied in jobs according to their qualifications, or previous job experience. They seem to prefer less-qualified working positions (census, 2001), while the majority of immigrant workers haven't any opportunity to find opportunities suited to their competency levels [5]. The second largest immigrant population in Greece comes from Bulgaria, according to Markova Eugene [7].The majority of Bulgarian Immigrants are women, in middle age, sometimes retired in Bulgaria, with secondary education even with tertiary education. Bulgarian women were the 6,1% (21.216) of the immigrants women in Greece (census, 2001) and financial problems are the main referred reason for migration. Migration rates depend on migration policy in Greece. In 2007, migration policy was simplified for Bulgarian people due to their participation in European Monetary Fund. In that state, the numbers of Immigrants coming from Bulgaria has raised in comparison with previous years [8].

SET CARE e-learning tool

SET CARE e- learning was an effort to meet the needs of care workers and family carers living and working in Greece. The training program was initially developed in Italy from Anziani e non Solo. ASPASIA training program is available in 7 languages and now through this transfer of Innovation project is adapted in Greek and Bulgarian. The Greek/Bulgarian version of the program includes new units: 6 units for managing people with Dementia and Alzheimer's Disease and a new unit for avoiding back pain.

The training program is consisted of 10 main units: 1 introductory unit, 5 units focusing on the basic issues of elderly people care, 3 units related to social and legal issues and 1 supplementary unit about basic knowledge on computer. More specifically:

1) Structure of the training program
2) Understanding the role of the carer
3) Relate and communicate
4) Most Common Pathologies ofolder people
5) Assisting People with Alzheimer's Disease
    5. 1) Understanding Memory function
    5.2) Getting to know about Dementia and Alzheimer's Disease
    5.3) Getting to know about behavioral Disorders in Dementia
    5.4) Care management of people with Dementia
    5.5) Simple activities for people with dementia
    5.6) The caregivers' burden
6) Take Care and Assist frail older people and people with dementia
    6.1) Physical mobility
    6.2) Personal hygiene
    6.3) Nutrition
    6.4) Nutrition for the older people
    6.5) Simple instructions about food Hygiene
    6.6) Management of Emergencies
    6.7) Simple instructions about the right body posture
    6.8) Housekeeping advices
7) Health system and social system in Greece
8) Migration policy in Greece/Legislation
9) The home caregiver as an enterprise
10) The use of the basic computer science and Internet
    10.1) Knowing computer components
    10.2) The use of the computer
    10.3) Learning more about Internet

Understanding the needs of paid carers

Initiallythe needs of a small sample of Bulgarian care workers who livedand worked in Greece were identified. In order to achieve this, we conducted interviews to following groups: Bulgarian women who work as caregivers and Greek family carers.

Bulgarian caregivers

The first attempt of interviewing Bulgarian careworkers living and working in Greece was not successful as women worked 24 hours in employer's house and they were unable to attend the interview. Instead we decided to call them to conduct a telephone interview and investigate their needs. Paid carers (7) from Bulgaria who care for a person with dementia were interviewed. Their mean age was 50 years old andmean years of education 11 years. The majority of women have encountered difficulties with their working in domestic sector because of Greek language. It is particularly difficult to "overcome the language barrier" and they are afraid of misunderstanding their duties. Another important issue, which has emerged from the interviews, was the course of the disease.

A major issue for the women who worked in the home care sector was the 24hours care, which was exhausting for them. They state that they need more leisure time, not just a day during the week. They all have admitted that patience is an important competence of caregiving and very important factor for the quality of care. Another common assumption is the fact that the stage of the disease influences the quality of communication and care. They also concluded that knowledge about the course of the disease, the symptoms and the pathology of Old Age would contribute to the care planning process.

The second focus group was conducted in Bulgarian Language with the help of Blagorodna Filevska, from Greek Bulgarian Cultural Association. We thought that it would be easier to conduct the interviews in Bulgarian language in order to investigate the educational needs of Bulgarian women who care for a person with dementia. The interviews conducted on Sunday with careworkers living in Greece for more than 10 years and have worked with older people and children. According to their opinion, the most important competences for care workers are communication skills and being able to be trusted by the main carer. They find it easy to learn management of practical issues, such bathing, feeding, and medication. They all insist characteristically that caring for a frail elderly is easier than caring for a child. An interesting finding is that although the majority of caregivers have back pains, they argue that they haven't encountered problem with the practical issues of care and they believe that there is not necessity for any change relating to care management.

The total number of participants insisted that they care for the older person as they would care for a family member. They realisethat knowledge about the progress of the disease and the pathologies of old age would be helpful for them and would simplify significantly their work. Neuropsychiatric symptoms of dementia seem to be a challenging problem for caregivers and make the communication with the patient very difficult. Neuropsychiatric symptoms and their management were the second most important issue, which they would like to learnin context of an educational program.

They have a positive attitude relating to their participation in a self study educational program. The use of computer or internet was not familiar for a little number of the participants. Though they would be happy to learn how to

use a computer, they are not willing to attend educational seminars out of the place that they work, but would be able to attend seminars on Sundays at the Greek Bulgarian Cultural Association. They prefer distance learning.

Family Carers

In an additional attempt to identify the training needs of paid carers, we interviewed 8 family carers, children and spouses. The majority of the sample considers that the nationality is a very important element of a foreign paid carer. Main family carers think that it would be important for the paid carer to have taken part in seminars, especially about practical issues (bathing, feeding), measuring of blood pressure, glucose and to be able to read drug prescriptions, guidelines for drugs and to understand Greek language. In cases where family has employed 2 or more paid carers, they think that this had happened due to difficulty in communication with the paid carer. An educational program is crucial for the quality of care and family caregivers are willing to give time to the paid carer in order to attend training program

According to family carers other issues that paid carers should learn about are: the progress of the disease, neuropsychological symptoms, communication with the patient, support and cognitive training, practical issues such as bathing, feeding, mobility tips etc.

Our results showed that Bulgarian women are not familiar with home care sector when started working as paid carers but they are willing to participate in a training program. The most important issues of such a program according to paidcarers view were: Greek language, olderpeople's pathologies, Alzheimer's disease and other dementias, managing communication with the elderly and his family. According to them training about practical issues is not high training priority, but they believe that it is important to receive this information. On the other hand, family carers give priority to management of practical issues as everyday care of the elderly person's nutrition and personal hygiene. They believe that communication and learning of Greek language are very important issues in care.

The aim of this study is to assessthe appropriateness, the usability and the acceptability of this innovation SET CARE program. A pilot phase has taken place in Greece and Bulgaria in order to assess the translated units and the newly developed units.

Method

Sample The sample of the piloting consisted of 21 people living in Athens and 10 people living in Bulgaria.

Pilot phase in Greece. The group was consisted of 16 paid carers from Bulgaria living and working in Greece. The majority of group (75%) aged between 46 to 65 years oldand 50% has completed the secondary educational level.37% of the paid carerswere living in Greece for 6 to 10 years and 25% for 10 to 15 years. 60% of the sample was living in the same household with the elderly who cared for.

The group of 16 careworkers was divided in 2 subgroups: Group A: receiving Instructions. This group consisted of 10 caregivers, mainly women (80%), aged between 46 to 65 years (80%). Experts, members of our working group provided instructions how to use the DVD and inform them about general principles of the project. Group B: receiving no Instruction. This group was not informed how to use the DVD In order to test its usability. Also the work group has notprovide any information about the structure of the training material in order to evaluate the content of programme. In this group 6 caregivers have participated, aged between 46 to 65 years (66%).

Pilot Phase in Bulgaria We run a second round of piloting in Bulgaria. In this pilot phase, two groups have been formed, one consisted of 5 careworkers, who were mainly women (80%), aged between 45 to 65 years (80%) and the majority of them was living in different household with the older people who cared for (60%). The second group consisted of 5 stakeholders.

Procedure Scientific staff of the project contacted paid carers from Bulgaria who work either in Greece or Bulgaria with frail elderly. 10 careworkers of the Greek Bulgarian Cultural Center participated in the study. Careworkers who visited the Dementia Day Care Centre and using the services of Home Care Program of Athens Association of Alzheimer's Disease were also included in the study. In all groups, users and stakeholders received the Demo DVD of SET CARE for a week and at the end of the week they answered the questionnaire assessing the educational material was administered.

Material

DEMO SET CARE

In pilot phasea demo of the SET CARE project has been distributed to participants. Athens Association of Alzheimer's Disease and Related Disorders, Balkanplan, 01pliroforiki, Anziani e non solo and Center of Family and Child, developed a first demo of SET CARE e-learning tool consisting of 4 Units for the purpose of the piloting. The units that were included in demo version were: 1) Unit 4: Pathologies of Elderly People 2) Unit 5b: Dementia and Alzheimer's Disease 3) Unit 6a: Mobility of Elderly 4) Unit 7: Health Services in Greece. Hard copy notes of each unit were provided as well, in order to provide extended information for each unit's subject.

Questionnaires

Two questionnaires were developed in order to assess the training material.The first questionnaire included the information for the epidemiological data of participants and its main aim was to investigate their expectations concerning an e-learning training program. The second questionnaire included information about the quality of the contents in regard to: 1) understanding 2) appropriate scientific knowledge, 3) learning of language 4) quality of audiovisual material 5) usability of the DVD and some additional information on the digital competences.

Results

Greek Caregivers

Careworkers have replied that they don't use Personal Computer often: 37,50% of the sample use computer only few times a month and only 18,75% everyday, 66, 67% of them has access on the Internet.

Another 43,75% of careworkers have replied that the program will assist them to better manageeveryday difficulties in care. 37,50% of the paid carers think that the training program will provide essential and contemporary knowledge on dementia and management of practical issues, as well learning on the use of PC. Additionally they think will have a chance to complete a vocational training, which help them achieve a better career and job opportunities (Fig. 1). Analysis of the data regarding the same question shows that there is differentiation among Group A (receiving instructions) and Group B (receiving no instructions). The subjects of these groups have different perception relating the way, whichthe program will help them. In Group A, 50% of paid carers think that they reap important benefits of this training program concerning several issues (awareness about dementia, vocational training, management of practical issues, learning to use PC) (Fig.2). On the other hand, in Group B 66,67% of the participants think that the program will primarily help them in management of everyday difficulties in caregiving and only 16.67% believe that the e-learning tool will offer them a multidimensional knowledge.

Figure 1. What do you believe SET CARE will offer you?

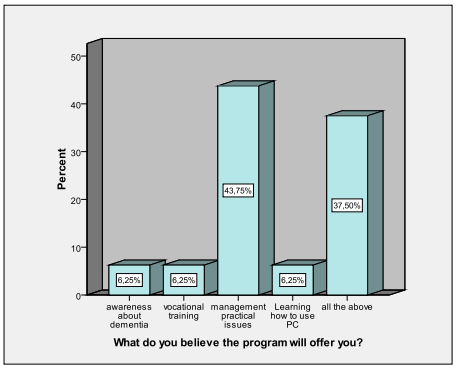
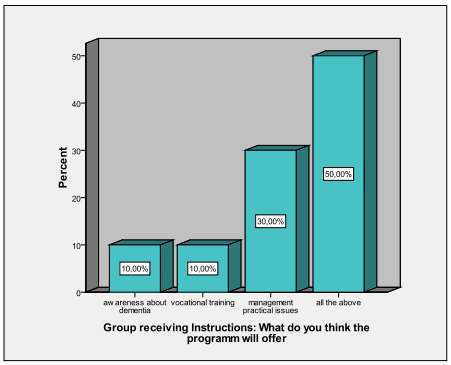


Figure 2. Expectations of the Program for the Group that has received instructions.



Units Assessment

Data of units assessment were analysed in Group A and Group B. According to Group A, 50% of the participants have assesed unit 4 "Aging pathologies in elderly people" as extremely easy to understand and is written in plain language, 20% very easy to understand, 20% easy enough and only 10% had some difficulty to understand the educational material. In Group B, although the participants had received no information or instruction on the use of the DVD, the majority of them had assessed unit 4 as easy enough to understand (83.33%). Similar replies have been provided for the unit 5b "Dementia and Alzheimer's Disease" (Figs.3,4), unit 6 "Assist in mobility of the elderly" (Figs.5, 6) and unit 7 "Health Services in Greece" (Figs 7, 8).

Bulgarian Careworkers

Paid Carers who live and work in Sofia have replied that they use Personal Computer everyday in a percentage of 60% and only 20% use PC rarely or have never used PC .All participants in the pilot phase had access on the Internet. 80% of careworkershave replied that the program will offer them vocational training and therefore better job opportunities and 20% of the participants think that the program will offer them awareness about dementia.

Units Assessment – Careworkers in Bulgaria

Participants assessed unit 4 "Aging pathologies in elderly people", unit 5b "Dementia and Alzheimer's Disease and unit 6 "Assist in mobility of the elderly" as extremely easy to understand and written in plain language .They assessed only unit 7"Health Services in Greece" as easy enough to understand.

Discussion

The pilot phase was aiming to assess the quality of the translated material for SET CARE project in Greece and Bulgaria: understanding, appropriateness of scientific knowledge, language learning, quality of audiovisual elements, usability of the demo DVD and acceptability by the care workers. Sample of paid carers and other stakeholders participated in this phase. The majority of the participants have cared for people with Dementia. As we have already discussed, 200.000 persons suffer from dementia in Greece and 100.000 in Bulgaria [1]. These numbers will increase in next decades. 90% of people with dementia are cared for at home by family members and paid carers. Paid carers in Greece are usually migrants from ex-Soviet union and Bulgaria. The profile of Bulgarian immigration as Konstantinova et al [9] describes is the following: "A woman in her 40's with higher education, married but alone in the host country (no children and husband with her), performing low-skilled work, residing in the host country for up to 3 years, sending up to 40% of her income back in Bulgaria, the main reason to emigrate – not sufficient funds from salary to support her family."

An important finding is that even if migrant women from Bulgaria have completed high educational level, they usually perform jobs, which are not relevant to their previous work experience. Caring for older people with dementia or other pathologies is not an easy job, even if the family is interested for a careworker without qualifications. People who work as paid carers face difficulties in communication with the family and the older person. They are facing difficulties in

managing practical issues such as mobility problems, personal hygiene and nutrition.Running the pilot phase for the project, we realized the great need for a training program that will simplify the daily routine of paid carers. Careworkers in Bulgaria and Greece admit that the program will offer them vocational training and sufficient knowledge about the management of everyday difficulties.

Figure 3. Assessment of Unit 5b for Group A

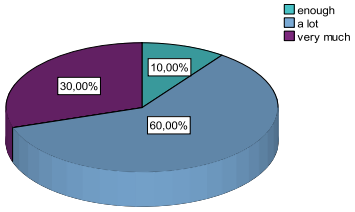


Figure 4. Assessment of Unit 5b for Group B

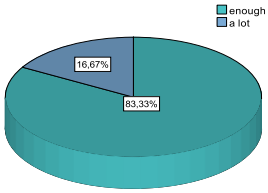


Figure 5. Assessment of Unit 6a for Group A

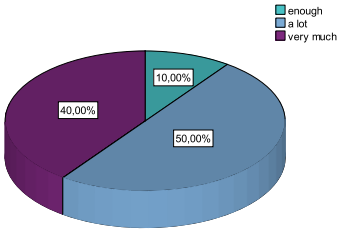
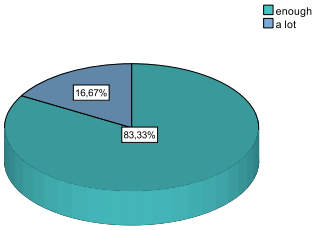
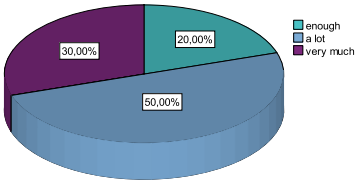


Figure 6. Assessment of Unit 6a for Group B





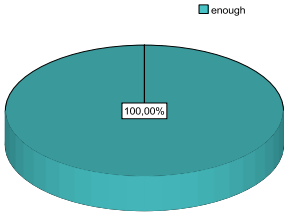


Figure 7. Assessment of Unit 7 for Group A

Figure 8. Assessment of Unit 7 for Group B

Another important finding is the assessment results among group A and group B. Participants who do not receive instructions on how to use the dvd, provided more neutral answers relating to usability of the dvd and the quality of the training material. On the other hand, participants who had been informed witha detailed presentation about the aims of the project and the e-learning tool, they providemore positive replies concerning the quality of contents, usability and appropriateness.

In conclusion, in Greece and Bulgaria, working as a paid carer is not an officially recognized job and women mainly undertake these tasks. In many cases, they provide much more work additionally to their caregiving tasks such as cleaning and cooking. These findings describe for the first time the training needs of migrant paidcarers in Greece and Bulgaria who works in home care sector. The study tries to identify the core issues in training that could assist paid carers at their work. This might be a first step to give voice to this population, who stays in a grey area and has no working rights.

The authors declare that they have no conflicts of interest.

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The quick Mild Cognitive Impairment screen: A new screening tool for mild cognitive impairment and early dementia

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Keywords: Screening -Dementia -Mild Cognitive Impairment

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Abstract

Objective: Differentiating mild cognitive impairment (MCI) from subjective memory complaints (SMC) and normal controls (NC) is important but challenging. Few short cognitive screens have sufficient sensitivity and specificity for use in busy clinic settings. This review explores the development and psychometric evaluation of a new, short (3-5 minute) instrument, designed to screen for MCI and early dementia, called the Quick Mild Cognitive Impairment (Q*mci*). This review examines the evidence published to date. Specific objectives include reviewing the content, concurrent and construct validity of the Q*mci* against a selection of other short cognitive screens and detailed global, functional and neuropsychological assessments. The Q*mci* is composed of six subtests: orientation, registration, clock drawing, delayed recall, verbal fluency and logical memory (LM). Initial validation studies in Canadian, Irish, Australian, Dutch and Italian populations show that the Q*mci* has excellent accuracy and is highly sensitive and specific at differentiating MCI from SMC, NC and early dementia. Cut-off scores, adjusted for age and education, and a new smartphone and tablet computer application are now available. The Q*mci* is externally validated in different settings including memory clinics, a movement disorder clinic, general practice and a rehabilitation unit, with translation and external validation in other languages underway. **Conclusion:** This review presents an exploration of a new and arguably much needed short, yet highly sensitive and specific, cognitive screen for use in clinics and general practice. Further research, with larger sample sizes, is now required to confirm its superiority over other short instruments designed to detect MCI.

Introduction

Neurocognitive disorders, as classified by the Diagnostic and Statistical Manual of Mental Disorders 5th edition, include mild cognitive impairment (MCI) and dementia [1]. Dementia, a major neurocognitive disorder, is defined by the presence of significant cognitive deficits that are two or more standard deviations from the mean, based on normative data, across one or more cognitive domains and accompanied by loss of social or occupational function, usually manifest as impairment in activities of daily living (ADL). MCI, a minor neurocognitive disorder, is defined as a mild, subjective, corroborated decline in cognitive function with evidence of modest impairment in cognitive performance, without evidence of impaired ADL, delirium or dementia [2]. The incidence and prevalence of neurocognitive disorders including MCI [3,4] and dementia [5-8] has increased in the face of societal ageing. Many challenges are associated with this, particularly in relation to their prompt diagnosis and management.

To diagnose neurocognitive disorders it is important to differentiate normal ageing from pathological processes associated with neurocognitive decline. Cognitive screening of symptomatic individuals followed by more detailed assessment with neuropsychological testing is the usual first step. As time is limited in clinical practice, busy clinicians require short cogntive screens [9, 10]. Few short screening instruments have been widely validated and questions remain regarding the ethical [11] and clinical benefits of unselected screening [12]. This is in part because of lack of sufficiently sensitive and specific screening tests to differentiate normal ageing from major and minor neurocognitive disorders [11,13].

Characteristics of an ideal short cognitive screen

Short cognitive screening instruments can be either direct neuropsychological or observer rated instruments. Effective screens must be short, easy to interpret, accurate and administered with only minimal supervision. Another important factor to consider is the setting. Different instruments may be more appropriate in different settings, depending on available time and resources. In busy clinical practice, particularly outpatients and general practice, short instruments are desirable. The utility of screening instruments is defined by two conditional probabilities, their sensitivity and specificity. The sensitivity of a test measures its ability to rule in disease, specificity its ability to rule out disease [14]. Short screens should have high sensitivity to reduce the rate of false negatives although a balance between both is desirable. Further assessment allows the exclusion of false positives and confirmation of the diagnosis. Another important measure is the accuracy of a screening test,

measured from the area under the curve (AUC) from receiver operating characteristic curves. The AUC is a function of the sensitivity and 1- specificity and is measured from 0 to 1. Scores above 0.5 indicate that the component (instrument) has better predictive power than by chance alone. A score greater than 0.8 suggests good accuracy, greater than 0.9 suggest excellent accuracy [15]. To use screening tests in clinical practice, cut-off scores, indicating transition points between different cognitive states, are useful. Since cognitive screening instruments provide a range of scores, the challenge is to select cut-off scores to maximise both sensitivity and specificity. Useful instruments should be responsive to change across the cognitive spectrum, from those with subjective memory complaints (SMC) [16] to MCI and dementia.

Several short cognitive screens are currently in use in clinical practice, each with their own advantages and disadvantages. Instruments can examiner directed neuropsychological or observer rated instruments. Some of the most commonly used screens, their advantages and disadvantages, are presented in Table 1. These include the widely used Mini-Mental State Examination (MMSE) [17], its standardised version (SMMSE) [18,19] and the particularly sensitive Montreal Cognitive Assessment (MoCA) [20].

Table 1. Comparison of the advantages and disadvantages of some commonly used cognitive (observer-rated versus direct neuropsychological) screening instruments.

Classification	Instrument	Advantages	Disadvantages	Timing	Reference
Observer-Rated	IQCODE	Short form available Comprehensive	Lengthy Difficult to score	10	n 2004 [21]
	AD8	Short Can be self-administered	Less comprehensive than IQCODE	2	Gavin et al., 2005 [22]
Neuro-psychological Instrument	MMSE (SMMSE)	Widely used translated & validated	Low sensitivity in those with high education; MMSE copyrighted for clinical use, does not assess executive function	5-10	Folstein et al., 1975 [17], Molloy et al., 1991 [18], 1997 [19]
	ADAS-cog (SADAS-cog)	Gold standard in clinical trials, includes 11 cognitive domains including praxis	Lengthy administration time	45	Rosen et al., 1984 [23]
	6CIT	Very brief, making it suitable for busy clinics, ward rounds	ttle ability to detect MCI	2-3	Brooke et al., 1999 [24]
	Mini-Cog	ttle education or language bias	Little ability to detect MCI, No challenging test of recall	4-5	Borsen et al., 2000 [25]
	GPCOG	Combines observer & neuropsychologic al components	Age & educational bias, informant required	4-6	Brodaty et al., 2002 [26]
	MoCA	Widely used translated & validated. High sensitivity specially in MCI	Low specificity, floor effects in advanced dementia, educational bias	10-12	Nasreddine et al., 2005 [20]
	ABCS 135	Short administration time. High sensitivity in MCI	Floor effects in advanced dementia, educational bias	3-5	Molloy et al., 2005 [27]
	TYM	Can be self-administered	Requires rater supervision	5-10	Brown et al., 2009 [28]

IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly; ADAS-cog=Alzheimer's Disease Assessment Scale-Cognitive section; MMSE=Mini-Mental State Examination; SMMSE Standardised MMSE; 6CIT=Six-Item Cognitive Impairment Test; MoCA=Montreal Cognitive Assessment; ABCS 135=AB Cognitive Screen; TYM=Test Your Memory

Objective

The objective of this review is to describe the development, validation and the psychometric evaluation of a new short cognitive screening instrument called the Quick Mild Cognitive Impairment (Q*mci*) screen, designed specifically to differentiate normal cognition from mild cognitive impairment (MCI) and early dementia. Specifically, this review examines the content, concurrent and construct validity of the new instrument by examining the results of data published to date.

The Quick Mild Cognitive Impairment screen

The Q*mci* is modeled on another short screen called the AB Cognitive Screen 135 (ABCS 135) [27]. The ABCS 135 has five subtests: orientation, registration, clock drawing, delayed recall (DR), and word fluency (VF) with a total score of 135. Although, the ABCS 135 is a sensitive and brief test to differentiate subtypes of cognitive impairment from normal cognition, analysis of its subtest scores suggested that much of the instrument did not enhance the discriminatory properties of the screen for MCI [29]. Further, while sensitivity was high, specificity was low. For these reasons the Q*mci* was developed to enhance the sensitivity of the ABCS 135. To do this, the weightings of DR and VF were increased relative to the total score and a new subtest, logical memory (LM), was added [30]. Scored out of 100 points, rather than 135, the Q*mci* places greater emphasis on VF and memory than its predecessor.

Table 2. Weightings of the subtests and total score of the Quick Mild Cognitive Impairment (Qmci) screen.

Qmci Subtest	Cognitive Domain	Description	Timing	Score
Orientation	Orientation	questions: What country, year, month, day and date?	1 minute	10
Registration	Working memory	word registration with three alternative word groups	30 seconds	5
Clock drawing	Visuospatial/ construction	Clock drawing within one minute	1 minute	15
Delayed recall	Episodic memory	word recall of the five registered words, recalled in any order	30 seconds	20
Verbal fluency	Semantic memory/languag	g task: naming a group of with three alternative forms	1 minute	20
Logical memory	Episodic memory	mediate verbal recall for a short story	30 seconds	30
Total score				/100

Table 3. Participant characteristics of studies validating the Quick Mild Cognitive Impairment (Qmci) Screen.

Country	Language	Setting	Sample size *Ongoing data collection	Sex % Female	Age Median +/-IQR	Education Median +/-IQR	Reference
Canada	English	Memory Clinic	965	57%	71 +/- 15	13 +/- 6	O'Caoimh et al.,2012 [30]
Ireland	English	Movement Disorder Clinic	84	38%	75 +/- 8	12 +/- 4	O'Caoimh, Foley et al.,2012 [37], O'Caoimh et al., under review
Ireland	English	Memory Clinic	551	66%	76 +/- 12	12 +/- 4	O'Caoimh et al.,2013 [35],[36]
Ireland	English	Geriatric Rehabilitation Unit	82	45%	81.5 +/- 6	12 +/- 3	O'Caoimh et al.,2013 [38], Daly et al., under review
Ireland	English	General Practice	63	67%	73 +/- 17	12 +/- 3	O'Caoimh et al., under review
Netherlands	Dutch	Geriatric Clinic	90	54%	75†	NA	Bunt et al., under review
Australia	English	Geriatric Clinic / Community Clinic	224*	63%	81 ± 9.5†	9.9 ± 2.3	Clarnette et al., under review
Italy	Italian	General Practice	62*	45%	76 +/- 9	14 +/- 7	Ilario et al., under review

† Mean/Standard deviation.

Table 4. Psychometric properties of the Quick Mild Cognitive Impairment (Qmci) Screen.

Country	Reference	Setting	Validated against	Prevalence of cognitive impairment %	Reliability r = x		Accuracy Area under curve = x	
					Test-retest	Inter-rater	MCI v Controls (*or SMC)	MCI v Early-mild dementia
Canada	O'Caoimh et al.,2012 [30]	Memory Clinic	SMMSE, ABCS 135	35%	0.86	NA	0.86	0.92
Ireland	O'Caoimh, Foley et al.,2012 [37], (O'Caoimh et al., under review)	Movement Disorder Clinic	MoCA	76%	NA	NA	0.92	0.87
Ireland	O'Caoimh et al.,2013 [35],[36]	Memory Clinic	MoCA, 6CIT	79%	NA	0.97	0.90 (0.81*)	0.95
Ireland	O'Caoimh et al.,2013 [38], (Daly et al., under review)	Geriatric Rehabilitation Unit	MoCA	57%	NA	0.77	0.76	0.72
Ireland	O'Caoimh et al., under review	General Practice	MoCA, GPCOG	51%	NA	0.89	0.91*	0.80
Netherlands	Bunt et al., under review	Geriatric Clinic	SMMSE	61%	NA	NA	0.86	0.73
Australia	Clarnette et al., under review	Geriatric Clinic / Community Clinic	SMMSE	89%	NA	NA	0.74	0.85
Italy	Ilario et al., under review	General Practice	SMMSE	56%	NA	NA	NA	NA

IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly; MMSE=Mini-Mental State Examination; SMMSE Standardised MMSE; 6CIT=Six-Item Cognitive Impairment Test; The General Practitioner Assessment of Cognition; MoCA=Montreal Cognitive Assessment; ABCS 135=AB Cognitive Screen TYM=Test Your Memory; NA=Not Available

Q*mci* Scoring and administration guidelines

The Q*mci* has a short administration time that if scored according to the guidelines should not take more than five minutes to complete. The Q*mci* includes six subtests, covering five cognitive domains: orientation, working memory, sematic memory, visuospatial and two tests of episodic memory, DR and LM. The subtests, scoring and cognitive domains of the Q*mci* are presented in Table 2.

Original validation

Tables 3 and 4 present the characteristics of studies validating the Q*mci* and the psychometric properties demonstrated by the instrument in each study, respectively. The Q*mci*, like the ABCS 135, was developed in a Canadian population. This first validation showed that the Q*mci* has superior accuracy over the commonly used SMMSE (AUC of 0.86 versus 0.67) [30]. It also showed that the Q*mci* has greater accuracy than its predecessor. All three instruments accurately differentiated MCI from dementia.

Cut-off scores

Prior to validation, the Q*mci* was collected in another outpatient database and a randomised controlled trial called the Doxycycline and Rifampin for treatment of Alzheimer's Disease (DARAD) [31], both conducted in Canada. These data were pooled with the original Q*mci* validation data set providing a large sample of patients and normal controls from which to develop cut-off scores. The preliminary results of this analysis suggest that a cut-off score of <60 produces the optimal balance between sensitivity (89%) and specificity (86%) for the presence of cognitive impairment (MCI or dementia) [32]. This combined data set also provided cut-off scores adjusted for age and education confirming the requirement to adjust scores, particularly for those aged over 75 years.

Content validity

Examination of the subtests of the Q*mci*, using the initial validation data set, showed that all subtests differentiated MCI from normal controls. However, not all subtests did this in a useful way, with AUC values ranging from to 0.56 to 0.80. LM was the most accurate subtest; word registration the least. All subtests distinguished MCI from dementia though orientation was now the most accurate with an AUC of 0.88. Median administration time was just over four minutes and the Q*mci* had excellent test-retest reliability [33].

In addition to demonstrating concurrent validity against the SMMSE and ABCS 135, validity has also been demonstrated against the MoCA. Although the MoCA is increasingly accepted as one of the short cognitive screens of choice, it is long, taking at least 10 minutes to complete [20], has low specificity and is considered by

some to be too difficult to use in those with significant cognitive impairment [34]. External validation of the Q*mci* in Ireland showed that it had a shorter administration time, excellent accuracy, comparable sensitivity and greater specificity than the MoCA at their established cut-off scores [35]. This is one of the first validations of the MoCA against an instrument designed specifically to screen for MCI. Even though the study was likely underpowered to show superiority, given the brevity and arguably easier scoring instructions of the Q*mci* relative to the MoCA, it suggests that the Q*mci* may be the better instrument to use as a scree in busy clinics or general practice. Additional concurrent validity was confirmed against another commonly used short cognitive screen, the Six-item Cognitive Impairment Test (6CIT) [36].

A further external validation in primary care in Ireland demonstrated that general practitioners, after a brief education session, had excellent inter-rater reliability compared to trained raters working in a memory clinic. The Q*mci* also compared well with a selection of instruments in this setting including the General Practitioner Assessment of Cognition (GPCOG) and the MoCA. Its brevity and ease of administration (no requirement for an informant unlike the GPCOG) suggest that it is useful in this setting. Other studies conducted In Ireland showed that the Q*mci* has good to excellent accuracy in patients with cognitive impairment (MCI and or dementia) attending a movement disorder clinic [37] and among inpatients in a university hospital rehabilitation unit [38].

Construct validity

Data from the DARAD trial was also used to assess internal consistency and the responsiveness of the Q*mci* to change over time [39]. It showed that the Q*mci* had high internal validity, was responsive to change over time and correlated with a detailed neuropsychological battery (Standardised Alzheimer's Disease Assessment Scale-Cognitive section - SADAS-cog), a global assessment of cognition (Clinical Dementia Rating scale - CDR) and an ADL scale (Lawton-Brody scale), suggesting that the Q*mci* could be substituted for a more detailed neuropsychological instrument in clinical trials [39].

Other research to date

The Q*mci* was also used as an outcome measure in a case-control study investigating the effects of a suite of lifestyle interventions on the progression of MCI [40], suggesting its predictive validity. It has also been used as an outcome measure in studies investigating the effects of anti-hypertensive medication on cognitive decline [41,42]. The Q*mci* is now translated into multiple languages and externally validated in Dutch and Australian populations. Validation is ongoing in Italy and Portugal.

Limitations of this research

Available studies investigating the Q*mci* have several limitations. The sample size of the external validations of the Q*mci* are small and likely underpowered to show superiority of the Q*mci* over equally sensitive instruments such as the MoCA. In addition to differences in sample sizes and settings between studies, the age, gender and educational profiles of participants in each study vary, limiting the ability to compare results and confirm trends. The prevalence of cognitive impairment was high across studies, ranging from 35% to 89%. High prevalence rates affect the sensitivity and specificity of instruments [43]. This predominantly refers to patients with dementia and likely reflects the nature of consecutive sampling in older adult clinics (memory or movement disorder), general practice surgeries and hospital inpatients in a geriatric rehabilitation unit. Another limitation is that the cut-off scores were derived from pooled data sets, potentially creating bias in that the baseline characteristics of participants may have been different. Age and education cut-offs were also derived from this data. This said, comparisons between databases showed only marginal differences in their demographic details and all three data sets were collected by the same principle investigator, Prof William Molloy, in similar samples in Canada, a large multi-cultural society.

Future research

The optimal extent, type and benefits of cognitive screening remain uncertain [12] with opposing views on the best way forward [44-46]. Undoubtedly there is a place for cognitive screening, especially in busy non-specialised outpatient clinics and in general practice. However,short, easy to administer, sensitive and specific cognitive screening instrument are required. To date, most studies have assessed the accuracy of screens in highly selected samples, usually patients attending memory clinics where the prevalence of cognitive impairment is generally high. Few instruments have been compared in general practice where the prevalence is low [47] and the utility of and need for these instruments is arguably at its greatest.

Although these data suggest the potential of the Q*mci*, its concurrent validity should be demonstrated against detailed neuropsychological assessment, other short screens and new diagnostic algorithms that take neuroimaging, blood and cerebrospinal fluid results into account [48]. Furthermore, to improve reliability the Q*mci* requires standardisation of its scoring instructions, a technique that has improved the scoring of the MMSE [18] and ADAS-cog [49]. Although there is some evidence that the Q*mci* was responsive to change over time [39] and useful in measuring conversion from MCI to dementia in a memory gym-clinic sample [40], it remains to be seen if the Q*mci* is useful in measuring and predicting progression from SMC to MCI and dementia. Normative data is also required to place screening scores in context of normal ageing [50]. A computerised application for smart phones and tablets has been developed (www.doctot.ie). Comparing the paper-based Q*mci* to the application is ongoing to confirm convergent validity. External validation of the Q*mci* is also ongoing in

other countries and settings. Both Dutch and Italian versions are being used in the FP-7 funded PERsonalised ICT Supported Service for Independent Living and Active Ageing (PERSSILAA, see http://www.perssilaa.eu; project number 610359) [51].

Conclusions

Population ageing has resulted in an increased prevalence of cognitive impairment, including MCI [3,5]. Unlike dementia, MCI is not associated with functional decline and there is increasing interest in early detection and intervention to prevention conversion to dementia [40,52]. Although screening large numbers of asymptomatic older adults is not recommended at present [12], targeted screening may be beneficial [44]. This review explores the development and the results supporting the use of the Q*mci* as a new, short cognitive screen for differentiating MCI from SMC and early- mild dementia. It presents the concurrent validity of the Q*mci* against a large selection of widely used and validated instruments. It also confirms construct validity against global cognitive and functional scales and the gold-standard assessment used in clinical trials, the Standardised ADAS-cog. Further research is required to confirm these findings.

The authors declare that they have no conflicts of interest.

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CSF biomarkers in the early diagnosis of Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a rapidly growing disease that affects millions of people worldwide, therefore there is an urgent need for its' early diagnosis and treatment. A huge amount of research studies are performed on possible accurate and reliable diagnostic biomarkers of AD. Due to its direct contact with extracellular space of the brain, cerebrospinal fluid (CSF) is the most useful biological fluid reflecting molecular events in the brain. Proteins and molecules that reflect the pathogenesis of the disease e.g. neurodegeneration, accumulation of Abeta, hyperphosphorylation of tau protein and apoptosis may be used as biomarkers. **Objective:** The aim of the current manuscript is to present the most commonly used CSF biomarkers for AD as well as novel biomarkers. **Conclusion:** Three CSF biomarkers, namely total tau, phospho-tau and Abeta42 are believed to have the highest diagnostic accuracy for early AD diagnosis and the ability to predict AD development in MCI patients. Moreover other biomarkers such as soluble APP, apoptotic proteins, secretases and inflammatory and oxidation markers, are believed to have increased future perspective.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease and the most common form of dementia in the elderly (about 60-70% of all dementia cases). Unfortunately, its prevalence has dramatically risen affecting about 44 million people worldwide, a number that is expected to double every 20 years, especially in developing countries [1]. Despite numerous clinical trials investigating this disease, there is still no effective treatment, therefore there is an urgent need for its' early diagnosis and treatment.

Definite diagnosis of AD is only.obtained at autopsy via the histological quantification of two AD hallmarks: brain amyloid plaques (that consist of amyloid-β [Aβ] peptide) and intraneuronal neurofibrillary tangles, that consist of tau protein [2]. Otherwise, for the possible or probable type of AD, diagnosis is performed with a certain percentage of error, which is increased in the early stages of disease, when the symptoms are unclear and difficult to interpret [1].

Mild cognitive impairment (MCI) is a clinical entity that has attracted clinical and research interest the last years, mostly due to the fact that MCI patients are at increased risk for developing AD, which might range from 10 to 30% per year [3]. It is believed that the early identification of the patients who will convert to AD may offer the opportunity of therapeutic intervention in the initial stages of the neuropathologic processes leading to AD, thereby substantially increasing the probability of therapeutic success.

Due to its direct contact with extracellular space of the brain, cerebrospinal fluid (CSF) is the most useful biological fluid reflecting molecular events in the brain, therefore proteins and molecules that reflect the pathogenesis of the disease e.g. neurodegeneration, inflammation and apoptosis could be used as biomarkers.

According to recent research studies [4-8], three CSF biomarkers such as Abeta42, t-tau, and p-tau are well established and are believed that have the highest diagnostic accuracy for early AD diagnosis. Moreover other biomarkers such as apoptosis markers, soluble APP, inflammatory and oxidation markers and secretases are studied and believed to have increased future perspective. This review will cover the most common CSF biomarkers that are used in AD diagnosis and some novel biomarkers that have been recently proposed.

Routinely Used Biomarkers

Beta-Amyloid (1-42) (Abeta42)

Abeta42 is a 42 amino acid peptide that is the main constituent of the amyloid plaques, one of the hallmarks of AD. It is cleaved from Amyloid Precursor Protein (APP) with the help of certain enzymes; beta and gamma-secretases. CSF Abeta42 levels are significantly reduced in AD patients compared to normal controls [9-11]. This is attributed mainly to its increased deposition in the amyloid plaques as significant correlation has been found between increased amount of amyloid plaques in the cortex and hippocampus and reduced CSF Abeta42 levels [12, 13]. Reduced CSF levels of Abeta42 were also observed in other dementia types, such as Lewy Body disease [14-15] Creutzfeld-Jakobs disease [16], vascular dementia and frontotemporal dementia [17]. However, these findings may be related to mixed pathology with dual pathology and overlap of the diseases. No significant correlation has been found between the duration of the disease and the patients' MMSE score [18]. Mattsson et al [19], who studied CSF biomarkers in MCI patients, found that CSF Abeta42 compared to t-tau and p-tau, is the most accurate biomarker for the diagnosis of the MCI patients that will convert to AD with 79% sensitivity and 65% specificity. This comes to agreement with van Harten *et al.* [20], who suggested that Abeta42 is the most accurate predictor of clinical progression in patients with subjective cognitive complaints and a more recent study by Ewers et al.[21], who found that CSF Abeta42 showed the best diagnostic accuracy among CSF biomarkers.

In contrary to most research studies, Jensen *et al.* [22] observed increased CSF Abeta42 levels in MCI patients compared to controls, but there were no follow-up studies on the MCI patients that converted to AD. On the other hand, in other studies, no significant difference was observed in the total CSF Abeta levels in AD patients and healthy controls [23, 24], therefore the levels of total Abeta were not considered an accurate AD diagnostic marker.

CSF Abeta42 was also found in the preclinical asymptomatic phase of AD and levels in the lower part of the reference range are strongly associated with future Aβ positivity [25]. In normal subjects high correlation was observed between blood and CSF Abeta42 levels, whereas no such correlation was observed in MCI and AD patients [26], which is believed to be due to the reduction of CSF Abeta42 levels. Therefore it can be derived that the accumulation of Abeta42 in the amyloid plaques of the brain causes the reduction of its' CSF levels. A similar study was performed on CSF and blood Abeta42 levels [27], which found no difference in the plasma levels of Abeta40 and Abeta42 in MCI patients that developed AD compared to MCI stable patients and healthy controls. On the other hand, CSF Abeta42 levels were reduced in MCI patients compared to controls. This difference was attributed by the authors to the fact that there is no correlation between blood and CSF Abeta42 levels. Although plasma Abeta42 levels cannot yet be considered as an independent AD marker, their changes might reflect AD conversion [28]. However, blood Abeta42 levels are not considered to be reliable compared to CSF Abeta42.

CSF Abeta oligomers correlated with cognitive decline in MCI and AD patients [29] and in particular Abeta40 oligomers were also proposed as a potential biomarker in AD [30]. Moreover, Aβ isoforms (Aβ 1-37 and Aβ 1-38) may help to differentiate AD from frontotemporal and Lewy Body dementia [31].

Total tau protein (t-tau)

Tau protein is the basic element of the neurofibrillary tangles (all 6 isoforms are located in these tangles) and is located mainly in the neuraxons, than dendrites and the cell bodies [32], Increased CSF levels of t-tau were observed in MCI patients [33, 9] and AD patients [10-11] compared to normal subjects. The increase in t-tau levels can be detected from the very early stages of AD and is stable as time goes by [10]. Moreover it has great sensitivity and specificity in the differential diagnosis of AD from normal aging (93% and 86% respectively) and depression, where the levels are normal [10]. In recent studies [34-35] elevated levels of t-tau and p-tau were observed in MCI patients that developed AD compared to MCI stable patients and normal control subjects. On the other hand, in MCI stable patients, no significant difference was observed in the protein levels between the exams and compared to healthy control subjects in the time period of 2 years [34].

Ivanoiu *et al.* [36] studied MCI patients and observed that t-tau levels were correlated more with memory function, whereas Abeta42 levels with the stage of the disease. Although it seems to be a reliable diagnostic tool in the differential diagnosis between MCI, AD and normal subjects, increase in t-tau levels is not considered an accurate diagnostic marker for AD, because it is increased also in other neurodegenerative diseases [37-38]. Increased levels of CSF tau protein were observed also in ischemic stroke [39] and trauma.

T-tau levels are very increased in Creutzfeldt-Jakob disease [40], small to medium increased in neurodegenerative diseases such as AD and normal in diseases without neurodegeneration [41]. Moreover t-tau and p-tau may be used for differential diagnosis of MCI from other diseases such as major depression [42]. A correlation between the CSF levels of t-tau and newly used techniques for AD diagnosis was sought. According to Toolboom *et al.* [43] the positive association between (18)F-FDDNP and CSF t-tau suggested that a part of the specific signal of (18)F-FDDNP in AD patients is due to tangle formation. Similar positive relationship between CSF tau/p-tau(181) with the amount of cortical amyloid was also observed [44].

Phosphorylated t-protein (p-tau)

The abnormal phosphorylation of tau protein has toxic actions and negatively regulates its ability to stimulate microtubule assembly. It is caused, to an extent, from the loss of balance between the activities of t-kinase and t-phosphatase [45-46]. Several forms of p-tau such as 396/404 [47], phosphorylated tau protein in threonin 181 [48] and phosphorylated tau protein in threonin-231 [49] were studied with ELISA method. Ishiguro *et al.* [50] observed that p-tau protein levels were significantly higher in AD patients compared to healthy subjects. The differentiation between the two groups was more easy and accurate using p-tau than t-tau. Therefore increased levels of p-tau are considered more reliable marker in AD early diagnosis. Together with isoprostane and the volume of the hippocampus they are useful markers in the differential diagnosis of MCI patients from healthy subjects, whereas the increase in p-tau levels and the reduction in Abeta levels are correlated with volume loss in the hippocampus [51].

In particular, p-tau in threonin-231 ($P\text{-}tau_{231}$), is considered to be the most accurate marker of MCI conversion to AD [52] with 80% specificity and 80% total diagnostic accuracy in distinguishing the MCI patients that will later convert to AD. It shows 90.2% sensitivity and 80.0% specificity in discriminating between AD and all non-AD disorders [53].

Combination of biomarkers

The combination of CSF Abeta42, t-tau and p-tau levels has 95% sensitivity and 83% specificity in determining the patients that will develop AD [24]. Similar results were observed by Andreasen *et al.* [54] and Hampel *et al.* [55] who observed total diagnostic accuracy of over 80%.

The combination of CSF proteins together with other diagnostic procedures can increase the accuracy of AD diagnosis. Low CSF Abeta42 and high t-tau levels combined with medial temporal atrophy are associated with increased risk of MCI conversion to dementia mostly AD. In particular the diagnostic value of CSF markers was 3-fold that of the medial temporal lobe alone [56]. The ratio CSF t-tau/Abeta42 protein shows promising results in predicting future MCI [57] and dementia [58] in cognitively normal older adults. Moreover, the sensitivity and specificity values of this ratio for AD diagnosis are 85.7% and 84.6% respectively [59]. It was also used to assess cognitive changes in patients after total hip/knee replacement surgery and the administration of spinal anesthesia [60].

The CSF ratio Abeta42/Abeta40 was an improved method of differentiating AD from other dementias compared to Abeta42 alone [61]. In large-scale MCI studies [53, 62] a CSF AD profile for t-tau and Abeta42 was proposed with a high accuracy of AD prediction in amnestic MCI patients (OR 26.8, 95% CI 1.6-456.4). Models that can accurately predict AD diagnosis based on CSF Abeta42 and p-tau were proposed [62-63). Several studies have suggested the combination of CSF proteins and Event-Related Potentials (ERP) waveforms as accurate diagnostic marker of MCI conversion to AD [64-66]. The combination of CSF and MRI markers was also studied with an accuracy of 91.8% in distinguishing between AD patients and controls. The combination was better than using either CSF or MRI biomarkers alone [67]. A low variability was observed in the CSF biomarkers during the day in AD patients, consequently continuous CSF measurement is considered accurate [68]. Therefore, combinations of CSF biomarkers can discriminate AD patients from normal subjects better than if they were used individually.

Novel biomarkers

Secretases

Secretases are proteolytic enzymes that cleave amyloid precursor protein (APP) to form Abeta. CSF Beta-secretase (BACE1) levels were significantly elevated in AD patients [69-70], AD-like biomarker profile patients [71] and in MCI patients compared to controls [72-73]. Moreover CSF BACE1 activity was found to be increased in ApoE4 carriers compared to ApoE4 non-carriers in both MCI and AD patients, showing an association between ApoE4 genotype and BACE 1 activity in MCI and AD patients [73]. On the other hand, in a more recent study no difference was observed in CSF BACE1 levels between AD, MCI patients and controls [74]. CSF BACE1 levels were associated with hippocampal atrophy in AD patients [75]. Plasma secretase activity was proposed as a potential biomarker in AD [76] However, in a new study by ADNI it was observed that neither CSF BACE1 levels nor sAβPPβ concentrations could be used to discriminate between healthy elderly and AD individuals [77].

Inflammation markers

The role of inflammation in AD is highly supported; therefore CSF markers of inflammation such as interleukins were also studied as AD biomarkers with inconsistent results. Several studies found that Interleukin-6 was increased in AD patients compared to healthy controls [78-80], whereas others found no statistical difference [81-83]. On the other hand, no significant difference was observed in interleukin-1 levels [84] and other interleukins such as IL-12 and IL-10 [85]. Other inflammatory markers such as Tumor Necrosis Factor-a (TNF-a) have also been studied with contradictory results; increased [86] or no difference between AD patients and controls. YKL-40 (chitinase-3-like protein 1) was found to be increased in AD patients compared to controls indicating that it might be helpful as an inflammatory biomarker in AD patients [87-88] and together with Abeta42 might be used as a biomarker for preclinical AD [89].

Apoptosis proteins

Cytochrome c is a vital part of the electron transfer chain and plays an important role in the process of apoptosis, through the activation of caspases. In this pathway, a variety of apoptotic stimuli cause the release of cytochrome c from the mitochondria, which in turn produces a series of biochemical reactions that ends in caspase 8 activation and as a consequence cell death [89-91]. Increased levels of cytochrome c and its release from the mitochondria may lead to mitochondrial dysfunction and destruction, that are correlated with oxidative stress in normal aging and also AD [92-96]. Papaliagkas *et al.* [64] found that AD-converters compared to MCI stable patients had a higher increase over time in CSF cytochrome c levels and the two groups can be discriminated with high accuracy (100% sensitivity, 75% specificity). Similar results were observed by the same research group for CSF Fas Ligand levels (FasL). Calpain, another protein involved in the apoptosis cascade was found increased in the CSF of AD patients [97].

Soluble APP (sAPP)

Low α- and β-cleaved soluble APP (sAPPα and sAPPβ, respectively) were observed in AD patients, especially those in advanced clinical stage suggesting that these markers might be related to the severity of the disease [98]. Soluble APP was studied also in MCI patients and it was observed that sAPPβ was higher in MCI patients that converted to AD compared with MCI stable patients suggesting a more accurate biomarker in AD diagnosis than Abeta42 [99]. According to the results of a current multicenter study [100] sAPPα and sAPPβ are promising biomarkers in separating AD from other types of dementias with high sensitivity and specificity. On the other hand, in early studies, no difference was observed in sAPPα and sAPPβ levels [101] between AD patients and controls.

Oxidative stress markers (Isoprostanes)

Oxidative stress has been implicated in AD pathogenesis. Markers of oxidative stress such as the lipid peroxidation enzyme isoprostanes have been suggested as AD biomarkers, with reliable results, supporting the involvement of oxidative stress in AD pathology. In particular CSF F2-isoprostanes were increased in AD patients [102-105] and baseline measurements could distinguish MCI patients or AD converters from healthy controls with 100% accuracy [106]. They were also related to cognitive decline in APOE4 carriers [107].

Neurotrophic factors

CSF Nerve growth factor (NGF) levels were significantly increased in AD patients compared to controls [108]. BDNF, a protein whose main role is to support the survival of existing neurons, and encourage the growth and differentiation of new neurons and synapses, was found to be associated with AD [109-110]. However further CSF studies indicated that it could be not taken as a marker of the disease [111-112], because it might be increased also in other neuropsychiatric disorders [111].

Other biomarkers

Cystatin C is believed to protect nerve cells against Abeta induced toxicity [113-114]. Lower CSF cystatin c levels were observed in AD patients compared to controls and correlated positively with Abeta42, Abeta40 and tau levels [115-116].Visinin like protein-1 (VILIP-1), a marker of neuronal injury, was also studied and higher CSF levels were observed in AD patients compared to controls suggesting its possible role as AD prognostic marker [117-118] Recent advances in the area of proteomics offer the potential to search for novel CSF biomarkers by using modern methods.

Conclusion

Although many studies and clinical trials have been performed on Alzheimer's disease, there is currently no effective treatment. One of the major concerns and research targets nowadays in the fight against AD is the finding of accurate biomarkers that will enable early diagnosis and as a result, AD treatment. CSF studies have provided promising results and measurement of Abeta42 and p-tau protein are already included in the new research diagnostic criteria for AD [119-120], however they should be further improved by novel CSF biomarkers. Therefore, CSF biomarkers have clinical utility in the differentiation between AD, MCI and normal subjects, and further discovery and validation is essential in order to improve early AD diagnosis and accelerate the development of new therapies.

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Assessment of health-related quality of life in elderly nursing home residents in Heraklion

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Abstract

Life expectancy extension is increasing the number of elderly people in Europe, 10% of whom now live in nursing homes. Thus the study of quality of life is important for Public Health. **Aim:** The aim of this study is the evaluation of the Health – Related Quality of Life (HRQL) in elderly residents of a nursing home, regarding: mobility, pain, sleep, energy, emotional reactions and social isolation. **Material and Method**: This cross-sectional correlation study was performed in a sample of 92 residents of a nursing home in Heraklion, Crete. Cognitive decline was evaluated with a Mini Mental test and data collection was carried out using the N.H.P. (Nottingham Health Profile) questionnaire. **Results:** Individuals with cardiovascular mobility problems have statistically significant lower quality of life as regards energy and pain. Individuals with hearing or vision problems have statistically significant worse quality of life as regards mobility and energy respectively. Those who have more than one health problem have statistically significant lower quality of life with regard to energy, pain and mobility. A statistically significant positive correlation was observed between age and energy, age and mobility and also between the years of living in a home and pain or sleep. No correlation was found between cognitive decline and the fields in question. **Conclusions:** The results corresponded with the findings of Southern European studies, as the highest levels of discomfort were recorded in energy, followed by mobility and emotional reactions, while the fields of sleep, social isolation and pain present the most effective management.

Introduction

The 1995 slogan of the American Geriatrics Society, “Add life to your years and not just more years to your life”, perfectly describes how important it is for older people to invest primarily in life quality and only then in longevity factors. Nowadays life expectancy is extended, increasing the number of elderly people. Today more than 10% of older people in Europe live in nursing homes. The study of their quality of life is therefore of great interest to public health. Taking this into account, the study object in this paper is the evaluation of the Health – Related Quality of Life (HRQL) in the elderly residents of a Nursing Home in Heraklion, Crete, regarding the following aspects: mobility, pain, sleep, energy, emotional reactions and social isolation. Their correlation with factors such as age or the length of time living in the home and the existence of cognitive decline was also studied in this epidemiologic cross-sectional correlation study, in which 92 of the 116 residents of the home took part. Cognitive decline was evaluated with a Mini Mental test and data collection was carried out using the N.H.P. (Nottingham Health Profile) questionnaire, which is internationally recognized for use in elderly people, with dementia or otherwise, living in nursing homes.

The term “old” as applied to an individual dates back to 1884, when the age of 65 was determined as the old-age borderline in Germany, purely for reasons of socio-political retirement programme management. Many other countries have adopted this definition since then, classifying individuals over 65 as old. Advanced old age involves gradual intense decline of human functions [1]. But the need to adjust to the restrictions of old age directly affects the quality of life of elderly people.

Many surveys deal with the quality of life of older people in general, such as the Survey of Health, Ageing and Retirement in Europe (SHARE), the British Household Panel survey (BHPS) and the English Longitudinal Study of Ageing (ELSA), the results of which were compared to post-analyses [2]. Today scientists agree that the concept of Quality of Life has always existed, but that it changes according to the prevalent life values, socio-economic conditions and the action of social forces. Researchers eventually invented measurement tools and developed quality of life evaluation methods, regarding health and social/psychological dimensions. However, questions of objective and subjective evaluation measures arose [3], while many scientists stress the need to combine these measures in order to evaluate human quality of life more comprehensively [4].

Many research tools have been used to measure various aspects of older people’s quality of life. However, it is difficult to evaluate their own subjective perception of their quality of life, when it is related to the measurement of healthy survival time as opposed to prolonged longevity accompanied by lack of health [5]. Health – Related Quality of Life (HRQL) is usually self-evaluated by the individuals participating in the study. HRQL is defined as the subjective perception of health, following the consequences of an illness or therapy affecting the physical, mental and social functionality of the individuals and their response to everyday activities [6]. Regarding older people, it seems that the evaluation of the subjective or perceived perceptions of their quality of life is very important, as it finally determines whether the individual is functional or not, despite the health problems caused by ageing [7]. For example, individuals with equal levels of mobility disability may have a different perception of their health condition and therefore differ in their adjustment, functionality and response to their social roles. Finally, the subjective perception of health conditions is what

is described as HRQL in the elderly. HRQL is one of the indices of non-nosological approach, for the evaluation of the health condition of older people [8]. Moving from the concept of Quality of Life of older people in general to the Health-related Quality of Life specifically, our interest is not focused on single health problems caused by ageing, but rather on the approach to the concept of healthy ageing as a stage of natural human evolution [9]. This approach is affected by the biological basis, the heredity and generally the morbidity of the individual and is evaluated by functional factors that express health, such as mobility and energy, pain, emotional reactions and social isolation, which are studied in this survey. However, when referring to the subjective evaluation of self-reported quality of life, one wonders how this is perceived by individuals with mental decline, such as patients with dementia.

Dementia is the decline of memory and cognitive functionality in comparison to the former level of the individual, which is drawn from the patient's history, the clinical examination and neuropsychological tests [1]. Alzheimer's-type dementia is a "gradual neurodegenerative disorder with characteristic clinical and neuropathological findings and gradual disorganization of human cognitive and functional abilities", but a necessary condition is that no other nosological cause is responsible for the dementia [10].

According to the World Alzheimer Report (ADI) in 2009, the occurrence of Alzheimer's disease was 10-15% in individuals over 75 years of age, and 1/5 in over-80s. Moreover, while in 2010 about 35.5 million people suffered from the disease, it is predicted that in 2050 at least 115.4 million elderly people will be affected. Subsequent epidemiological surveys [11] indicated a rate of 1% to 8% in the population over 65 years of age suffering from moderate to serious dementia. It was also underlined that these rates are doubled for every 5-year period over 65 years. In the same study it is mentioned that 60 – 70% of older people living in homes suffer from dementia. It is therefore necessary to educate health professionals in the use of dependable tools to identify the disease, as early diagnosis is cost-effective and contributes to the improvement of the future quality of life of the old person.

Necessity of the study: Although sufficient tools for the evaluation of the subjective perception of older people for the Health-related Quality of Life have been developed, the application of these tools has not yet provided many surveys. Moreover, even at international level there are not enough studies focusing on the HRQL of older people living in homes [12].

Aim and goals: The aim of this study is the evaluation of the HRQL of the residents of the Nursing Home, in Heraklion, Crete, as to the following aspects: mobility, pain, sleep, energy, emotional reactions and social isolation, in order to understand which of these HRQL aspects require improvement interventions. A separate aim of this study is to evaluate the correlations of the above HRQL aspects with:

- The socio-demographic characteristics of the residents of the home.
- The subjective perception of their health condition.
- The decline of their cognitive functionality.

The study of the results of the above correlations is expected to help determine the directions in which targeted interventions should be carried out.

Research questions – research hypothesis

The research hypothesis is that the HRQL of the residents of the Nursing Home in Heraklion, Crete, is at a level which can be improved under certain conditions.

More specifically, the definition and recording of the existing situation is a precondition for this study. It is also an incentive for the study of further variables affecting the HRQL of the elderly people in the home. Thus the following questions are studied:

A) The basic research question:

"How do you evaluate the HRQL of the residents of the home today and which aspects present the largest margin for improvement?"

B) The individual research questions:

Is the HRQL of the elderly residents of the home, regarding the aspects: mobility, pain, sleep, energy, emotional reactions and social isolation, related with:

1. The socio-demographic characteristics of the residents of the home.
2. The subjective perception of their health condition.
3. The decline of their cognitive functionality.

Material and Method

The present study was conducted in 2014 in the Nursing Home in Heraklion, Crete. The reference population is the total of 116 residents of the home who were approached to take part in the study, of whom 92 individuals agreed to participate. The elderly people who took part in the study were informed of the aim of the study and the way it was conducted and were asked to give their written consent to participate voluntarily. The selection criterion was the fact that the participants were residents of the Nursing Home of Heraklion, Crete at the time the research was conducted. An epidemiological cross-sectional correlation study was planned. In studies of this type, the data selection is carried out once and the results are considered to be representative only of the specific period of time in which the research takes place [3]. HRQL is correlated with socio-demographic variables, the decline of cognitive functionality, and health factors. Furthermore, all the data come from only one home, which is considered to be an independent elderly care unit, so this research is a case study.

The data collection tool and their completion

For the data collection of the HRQL evaluation, the elderly people were asked to complete the NHP (Nottingham Health Profile), an internationally accepted questionnaire of 38 questions. This questionnaire was created by Hunt, Mc Even and Mc Kenna [13].

The N.H.P in its first part approaches 6 aspects of evaluation of the Health related Quality of Life (mobility, pain, sleep, energy, emotional reactions, social isolation), on which the present study focuses. This use of the N.H.P. has been found to be suitable for the evaluation of the HRQL (and not Quality of Life in general) in older people who live in homes [14] (Tabali et al. 2011). Moreover, the N.H.P. has been found to be effective for use with elderly people with mental decline up to a moderate degree [15]. Therefore, as the Nursing Home residents all have perfect, good or moderate mental ability, the N.H.P. was found to be a suitable tool for data collection in the present survey.

Although this questionnaire was initially designed as self-completed, it has also been used as completed by specialized research staff, with equally good evaluation as a data collection method [14]. So, for the needs of the present survey the questionnaire was completed by the researcher, following a personal interview with each elderly person. The interviews took place in the home in an environment of individualized approach for the protection of personal data.

Permission to use the N.H.P was requested from the copyright holder, the research company Galen Research, and granted following submission and approval of the research protocol. Permission to use the Greek version was also granted by the Greek researchers A. Vidali and M. Siggelaki, who carried out the translation and adjustment of the NHP to Greek conditions [16].

The Mini Mental State Examination (M.M.S.E.) is the most widespread evaluation scale of mental functions decline. It is a brief and easy-to-use tool with high sensitivity and specialization. This questionnaire evaluates orientation in time and space, immediate or late recall, attention, calculation ability, use of language, and visual-spatial abilities [17]. The elderly residents of the Home are frequently tested for their cognitive functionality using the M.M.S.E. test, Moca and Hindi Mental examination test for illiterate or highly educated older people respectively. The most recent data in the social service records of the Home, indicating the present situation of the residents, were used for the collection of data for the evaluation of the cognitive functionality of the elderly people who participated in the research.

Permission for the conduct of this study was requested from the Nursing Home management. The Director of the Home approved the research protocol. The elderly people provided a signed agreement to participate voluntarily in the research. Before signing, they were thoroughly and clearly informed, according to the W.H.O. Bioethics and Ethics rules 2000 [18] for the protection of the integrity and personal data of research participants.

Results

The authors of the questionnaire suggest statistical analysis with non-parametric tests: Mann-Witney, Kruskal-Wallis [16]. The differences in the scores in each sector of each category that appears in the sample were tested with the Mann-Whitney test for two independent samples or the Kruskal-Wallis test for more than two. Every statistically significant result in the Kruskal-Wallis test was designed for post-hoc controls to follow two by two, with Bonferroni correction (however, no such results were found). Non parametric Spearman linear correlation coefficient was used for the correlation of continuous variables with ordinal variables.

All the controls are two-way, controlling whether the correlation of the variables differ at a level of statistical importance α=5%. In this questionnaire the answers were “YES” or “NO” and the internal consistency of the questionnaire was controlled in each HRQL aspect with the Kuder-Richarson index (KR20). The total score for each sector of the questionnaire was calculated after the answers to the questions were transformed into numerically weighed values 1-100.

The internal consistency of the questionnaire was controlled in each sector with the Kuder-Richarson index (KR20) which was at high levels, ranging from 0.63 to 0.88. The sectors of HRQL / age / years of life in the home and median – IQR are described Table 1 below.

The following table shows the older people’s marital status. Parenthood and the rates of cognitive decline are shown in the following tables. Table 4 below describes the decline of older people’s cognitive functionality. Table 5 shows subjective and objective health conditions. However, the subjective perception of their health condition is described in Table 6. Correlations of age - years of life in the home with sectors of the Health Related Quality of Life of elderly residents are shown in the following tables, where the non parametric Spearman linear correlation coefficient was used.

No statistically significant correlations with any of the HRQL sectors in question were found with regard to the remaining sociodemographic data. Moreover, no statistically significant correlation was found between the levels of cognitive functionality and the HRQL sectors in question. In contrast, health problems seemed to affect some of the individual HRQL sectors. Considering the results of the Tables above, the need to assess the correlations between health problems and the six sectors of the questionnaire became clear. The relevant results are shown in Table 8.

In total, individuals with multiple health problems have statistically significant higher values (worse quality of life) in the sectors of energy (p-value=0.004) pain (p-value=0.002) and mobility (p-value=0.001). as shown in the following table. Finally, Table 10 presents the correlations of the HRQL parameters with the levels of cognitive functionality decline

Discussion

The study and sample populations are not sufficient to provide conclusions on the HRQL of elderly people living in homes in general. The conclusions concern only the population of the specific home. Moreover, as the data collection is a cross-sectional study, these results can give conclusions only for the specific time. Finally, the isolation of some variables for the correlation with the HRQL is extremely difficult. For example, age interacts with various other intermediate and confusing factors, such as the ageing process itself, which also affect HRQL.

Table 1. Sectors of HRQL / age / years of stay in the Home and Median - IQR

HRQL Domains	Median (IQR)
TEN energy	63.2 (24.0, 100.0)
TP pain	12.9 (0.0, 53.6)
TEM emotional reactions	44.2 (19.1, 63.6)
TSL sleep	38.5 (0.0, 72.7)
TSO social isolation	22.5 (0.0, 42.7)
TPM mobility	44.7 (21.4, 67.2)
age (years)	82.0 (73.0, 88.0)
Stay in the Home (years)	3.0 (2.0, 6.0)

Table 2. Older people's marital status

Marital Status	N %
single	18.5%
widowed	56.5%
married	13%
divorced	12%

Table 3. Parenthood

Children	N (%)
yes	61 (66.3)
no	31 (33.7)

Table 4. Decline of cognitive functions

Cognitive functions decline	
M.M.S.E.	N (%)
moderate	52 (56.5)
good	35 (38.0)
perfect	5 (5.4)

Table 5. Subjective – Objective Health Conditions

No Health Problem (Subjectively)	N (%)
yes	16 (17.4)
no	76 (82.6)
Report of Health Problem (objectively)	
no	12 (13.0)
yes	80 (87.0)

Table 6 Subjective Perception of Certain Health Problems

Cardiovascular	N (%)
no	66 (71.7)
yes	26 (28.3)
Diabetes	
no	74 (80.4)
yes	18 (19.6)
High blood pressure	**N (%)**
no	80 (87.0)
yes	12 (13.0)
Mobility	**N (%)**
no	53 (57.6)
yes	39 (42.4)
Hearing	
no	82 (89.1)
yes	10 (10.9)
Vision	
no	80 (87.0)
yes	12 (13.0)
Other (further)	
no	60 (65.2)

yes	32 (34.8)

Table 7. Spearman non parametric linear correlation coefficient Correlations of age - years of stay in the home with Health Related Quality of Life sectors

	Age		Years in the foundation	
	Spearman ρ	p-value	Spearman ρ	p-value
TEN	0.28	0.008	0.17	0.103
TP	0.06	0.601	0.26	**0.014**
TEM	0.15	0.172	0.04	0.704
TSL	-0.07	0.520	0.21	**0.049**
TSO	-0.06	0.588	0.05	0.651
TPM	0.36	0.001	0.01	0.962

Table 8. Median, 1st and 3rd quarter (IQR) and statistically significant correlations between health problems and the six sectors of the questionnaire.

	Cardiovascular		
	no	yes	
	Median (IQR)	Median (IQR)	p-value
TEN	62.0 (24.0, 100.0)	100.0 (60.8, 100.0)	**0.049**
TP	11.2 (0.0, 46.9)	27.0 (5.8, 80.3)	**0.048**
TEM	42.2 (14.0, 62.5)	50.4 (31.5, 68.2)	0.174
TSL	37.8 (0.0, 72.7)	53.5 (12.6, 77.6)	0.207
TSO	22.5 (0.0, 42.7)	36.1 (19.4, 42.1)	0.862
TPM	33.8 (12.7, 66.6)	50.9 (41.9, 67.2)	0.058

	Hearing		
	no	yes	
	Median (IQR)	Median (IQR)	p-value
TEN	63.2 (24.0, 100.0)	100.0 (60.8, 100.0)	0.066
TP	12.9 (0.0, 53.6)	17.3 (5.8, 46.9)	0.562
TEM	43.7 (19.1, 62.0)	59.2 (26.7, 83.0)	0.293
TSL	37.8 (0.0, 72.7)	77.6 (22.4, 77.6)	0.098
TSO	22.0 (0.0, 42.7)	42.1 (22.0, 42.1)	0.310
TPM	42.8 (20.5, 66.0)	66.6 (55.5, 78.7)	**0.015**

	Mobility		
	no	yes	
	Median (IQR)	Median (IQR)	p-value
TEN	60.8 (0.0, 100.0)	100.0 (60.8, 100.0)	**0.003**
TP	5.8 (0.0, 24.7)	28.7 (12.9, 71.3)	**0.001**
TEM	41.1 (13.0, 54.0)	52.8 (24.6, 83.0)	**0.020**
TSL	28.7 (0.0, 65.1)	51.0 (12.6, 77.6)	0.101
TSO	22.0 (0.0, 42.1)	37.0 (19.4, 64.7)	0.375
TPM	22.5 (12.7, 56.1)	62.1 (44.1, 78.7)	**<0.001**

	Vision		
	no	yes	
	Median (IQR)	Median (IQR)	p-value
TEN	63.2 (24.0, 100.0)	100.0 (80.4, 100.0)	**0.043**
TP	12.9 (0.0, 48.9)	26.9 (2.9, 92.1)	0.260
TEM	43.7 (17.0, 65.5)	50.4 (32.6, 60.9)	0.568
TSL	37.8 (0.0, 72.7)	60.8 (28.0, 77.6)	0.153
TSO	22.0 (0.0, 42.7)	36.1 (10.1, 42.1)	0.948
TPM	43.8 (20.5, 67.2)	55.5 (33.2, 62.5)	0.573

Table 9 Statistically significant correlations between multiple health problems and the six sectors of the questionnaire.

	Health problem		
	no	yes	
	Median (IQR)	Median (IQR)	p-value
TEN	30.4 (0.0, 62.0)	63.2 (38.0, 100.0)	**0.004**
TP	0.0 (0.0, 8.2)	19.5 (0.0, 59.0)	**0.002**
TEM	31.5 (0.0, 57.9)	45.0 (22.2, 63.6)	0.136
TSL	17.5 (0.0, 54.6)	43.4 (6.3, 72.7)	0.232
TSO	21.1 (0.0, 40.3)	35.3 (0.0, 42.7)	0.444
TPM	21.6 (0.0, 22.1)	50.9 (22.7, 68.1)	**0.001**

Table 10 Correlations between cognitive functionality decline and the six sectors of the questionnaire.

	Cognitive functionality decline M.M.S.E.			
	medium	good	excellent	
	Median (IQR)	Median (IQR)	Median (IQR)	p-value
TEN	63.2 (38.0, 100.0)	63.2 (24.0, 100.0)	24.0 (24.0, 36.8)	0.468
TP	12.9 (0.0, 48.9)	14.8 (0.0, 63.9)	10.0 (0.0, 26.3)	0.833
TEM	49.9 (19.1, 66.2)	41.3 (19.1, 59.8)	43.1 (41.4, 48.0)	0.793
TSL	37.8 (6.3, 68.9)	50.4 (0.0, 77.6)	55.9 (0.0, 71.3)	0.696
TSO	36.1 (0.0, 42.7)	22.0 (0.0, 57.3)	19.4 (16.0, 22.0)	0.528
TPM	46.2 (22.0, 67.2)	46.2 (21.8, 69.4)	20.5 (11.2, 21.4)	0.100

The profile of the old people described in the results regarding their marital status and their health conditions is in accordance with the sample of other researchers such as Scammbler & Blane,Murrell & Meeks [19,20]. Studies of nursing homes in Europe showed considerably lower HRQL in older women compared to men living in homes, mainly regarding the field of pain in Germany and the fields of energy and mobility in Finland, based on the measurement of the N.H.P. questionnaire [12, 24]. In the study of the Nursing Home in Heraklion there was no correlation between sex and any sector of the HRQL.

There is a difference between the subjective perception of health and the objective health condition according to medical attestation. This is in accordance with the results of German studies [21,22]. Cognitive functionality decline has shown no statistically significant correlation with the HRQL as shown in table 10. This is in disagreement with studies [23] which have a sample that includes enough people with only a slight decline of cognitive functionality, who therefore evaluate their quality of life more objectively. In table 8, the aggravation burden of the HRQL by sector of health problems is presented. The results show an aggravation burden of the HRQL and match other studies [12]. Ranking the aggravation burden of the HRQL, it emerges that older people with cardiovascular problems have a moderate aggravation burden in the sectors of energy and pain. They are followed by persons with decline in hearing and vision and in the sectors of mobility and energy respectively. Stronger discomfort in more sectors is felt by older people who have mobility decline, in the sectors energy, pain, emotional reactions and mobility. Persons with hearing and vision decline also have statistically significant worse quality of life in the sectors of mobility and energy respectively. The results of the ranking of the aggravation burdens of the HRQL are in accordance with a study by Noro A. & Aro. S. conducted in Finland [24].

Elderly people with co-morbidity problems have the worst evaluation of the HRQL, mainly in the sectors energy/pain/mobility, as shown in table 9. This is in accordance with a study by Kane & Kane (1981) [9]. The highest levels of discomfort - scaled - are in the sector of energy, followed by mobility and emotional reactions, as recorded by other studies [12,25]. Sleep, social isolation and pain show the lowest levels of discomfort in general. However, in studies of other homes, mainly in the Netherlands, the field of pain does not seem to be managed effectively, with the exception of geriatric psychiatric homes [25, 26].

Conclusions

It can be said that elderly people over 80 years of age who have no partner and have chronic health problems and co-morbidity, choose to live in a Nursing Home in order to have better quality of life. The difference between subjective and perceived health condition is an index of the old people's adapting behavior to the health problems, which they accept as a natural consequence of ageing. Possibly the same gradual adaptive behavior of elderly to cognitive functionality decline contributes to the fact that no correlation with the latter is proved. HRQL is also evaluated subjectively by the individuals themselves.

It has to be said that it is worth investigating further the relationship between the role of drugs and the HQRL. In particular, there is lack of data regarding the relationship between the ability of drugs to influence mood and the subjective perception of elderly people about their particular domains of HRQL. As the highest levels of discomfort are in the sector of energy, followed by mobility and emotional reactions, a need for physiotherapy and psychological support of elderly people in homes is highlighted. Sleep, social isolation and pain show the lowest levels of discomfort. This is an indication of good functioning of the Nursing and Social Service. However, the effectiveness of these services seems to decline over time in the field of sleep, if you look at the results regarding the years of living in the home.

This last conclusion, however, is not safe, as there is interaction with the factor of age increase, and further study is needed. The correlation of HRQL sectors in a home with other health parameters, e.g. life expectancy and areas of psychiatry, is of interest for exploration in new studies.

The authors declare that they have no conflicts of interest.

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The emotional brain in the classroom

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Abstract

Aim: This paper aims at explicating how emotional processing regulates educational processing and accounts for the different reactions of the learners to new educational situations. Learning presents with a twofold expression, namely cognitive and emotional competency. It is the latter that needs to be more fully addressed, considering that nature and nurture, cognitive, affective, and environmental factors are interwoven during the schooling years of a person's life. Considering that school constitutes a comprehensive social environment, emotional competency allows learners to meet its requirements and shapes their personality and temperament. Cognitive neuroscience methods have provided an explicit locus of the affective part of the brain, i.e. the limbic system, and have shed light on the functioning of the amygdala and the hippocampus. Stress or fear may hamper the connections of this part of the brain with the frontal cortex thus compromising responses to learning, social judgment, and cognitive performance. **Conclusion**: A type of chain effect is created emerging from stressful feelings in the classroom, which disturb the attention skills balance, hence affecting learning capacity.

Introduction

School is a learning community, encompassing all potential learners. It offers systematic opportunities to gain experience, to experiment, and to actively participate in and process knowledge. Most importantly, school generates circumstances for communication, interaction, socialization, and integration of all students. Its mission pivots around qualitative characteristics. In this sense, it offers learning and co-operation skills, so as for everyone to respond to their personal life expectations, while developing the concept of solidarity. Among others, school aims at providing students with favourable learning and evolution prerequisites, in order for them to become adept at actively participating in social life. Learners, through their daily school activities, learn and appreciate their abilities and deficiencies, while cultivating their personalities. Through appropriate pedagogical and psychological support and guidance, they can approach self-perception, and familiarize themselves with the notions of recognition and refusal. Students need to be equipped with elaborate cognitive and emotional competencies as a means to perceive reality from multiple perspectives, collect and process target-related information, select and assess alternative methods of action, evolve both at a personal and a collective level.

In order for the essential goals of contemporary education to be achieved, the focus should be transferred onto the interrelation of the three constituent parts of every educational system, i.e. the educator, the students, and the parents. Nonetheless, it is the educator who is expected to perceive the dynamics of the family-school system, observe the generation and perpetuation of behaviours on behalf of the students, provide concrete explanations for their conduct, and suggest appropriate intervention. The interaction of the three parties is bound to cause chain effects, often beyond control. Evidently, the educators need to accept the challenge and learn how to decipher the communication messages, take notice of the group interactivity, measure it against affective standards, handle the negative feelings and disputes in the classroom, aspire to converge opposites, and define the rules of conduct in the classroom based on the personal developmental targets of the students.

Within such an educational system, which is founded upon the active participation of the learner in the process of individual learning, the aim is to mobilize personal research interest and to approach novel knowledge through a different lens. In this procedure, the educator does not transmit knowledge nor do they provide answers which can be applicable to all issues, but rather they coordinate the learning process and function as a catalyst too, while becoming a prototype for their learners to imitate.

The teacher

"If (the teacher) is indeed wise, he does not bid you enter the house of his wisdom, but rather leads you to the threshold of your own mind." [1] The roles a teacher assumes and the tasks they need to fulfill before, while, and after the lesson, are overwhelmingly multiple, complex, and demanding. Not only are they responsible for transmitting knowledge, but they are required to interact with all of their students simultaneously and multi-dimensionally within a pressed time frame, while securing the smooth materialization of the teaching-learning process. The attempt to reach a converging point with regard to learners' individual variations loads the teacher with an additional challenge, because teaching is addressed to a whole group of students whereas learning is individually mastered. If a classroom were paralleled to a natural reserve, it is the educator who conditions, moderates, and affects the classroom microclimate [2], whereby the group and individual efforts to absorb learning can flourish. The teachers who assist their students in their learning attempts and transform teaching into an experiential journey are liable to leave their mark on these people's lives. With this belief come the 'great

expectations' of all students that their teacher masters their subject matter, is eager to adapt to novel educational situations, caters for their needs, differentiates teaching approaches in order to encompass affected learners, encourages them all to proceed, engages them all in the same process, provides constructive feedback, safeguards them when taking risks, respects their personality, protects them, and is responsible for them and their progress. Encouragement and reward, peer collaboration, acceptance and support [3], along with reasonable decision making and successful problem solving [2] seem to be key elements to a successful and fruitful learning environment [4].

Promoting a positive and supportive classroom setting, as a result of a rigid classroom management plan [2], constitutes yet another puzzle to be solved. Evidently, before a lesson is conducted, the teacher needs to have paved the ground by means of identifying their students' emotional and situational status and discerning what they are thinking [5-7]. Intentionally adopting a novel model of instruction [5] without evaluating the affective charge of the target group equals almost discarding the presence of the students as whole personalities. Possessing or developing sensitive antennae to capture the signals transmitted by the class will grant the teacher the opportunity to change their posture, gaze, and tone of voice, probably switch to a more entertainer-performer role, and modify their pre-designed activities. Within a carefully designed framework where stressful feelings will not easily emerge and attention balance skills will not be compromised, students can be guided to confidently cultivate the physical, social, emotional, and intellectual competencies in concert. Perhaps a teacher's most challenging task is to establish a link of school knowledge with life after school requirements, and equip students with the ability to set feasible goals, make the necessary moves towards its achievement, develop flexible thinking in order to provide alternative solutions, and finally assess their choices [2].

The learner

If the profile of a learner were to be delineated, a threefold outline should be produced shedding light onto the age, learner differences, and motivation [8]. Young children, adolescents, and adults learn in a different manner, due to the brain plasticity which displays distinct variants and improves linearly with age [9]. Almost regardless of individual brain differences, each brain can potentially improve and change, it can be reshaped, and this is possible through teaching and learning [9, 10]. From birth and well into childhood, neural connections in the brain are generated and subsequently rapidly increased, a process called synaptogenesis [9-11]. Learning, memory, and overall cognitive performance during that period are strengthened and improved [9]. Obviously, exposure to the process of explicit training of the brain in the acquisition of new knowledge reinforces and changes neural activity, whilst enhancing plasticity [5, 10], hence the view that learning actually occurs in the brain of the learner [6]. The inherited genes, the environmental experience, as well as the frequent use of the newly created synapses are the determining factors for synaptic pruning [9, 10], i.e. the extinction of unused neural connections to the benefit of the more frequently used ones. Apart from the much studied cognitive networks, the brain has developed the limbic system, the affective part of the brain, which has been implicated in memory functions, is partly responsible for influencing attention, memory, and social processing [6, 12]. With respect to attention, students are particularly favoured by this attribute of the emotional network, because not only are they able to acquire knowledge, retrieve information, and recall events, but they can also regulate their emotion and behaviour [12, 13]. Furthermore, cognitive processes, such as memory, can be enhanced when they are triggered by positive emotions [12, 14]. As far as the social implications of the affective brain, people based on their previous experience and cultural background are in a position of making hypotheses, create new experiences, and project novel emotional reactions to specific events [6].

Contrary to the theory of 'critical period' or 'most sensitive period' which posits the impossibility of skill acquisition beyond a time limit in a child's life [9-11], it has been proved that what is actually critical is the exposure of the brain to language and communication environments [9]. The brain continues to develop and be moulded with age. It is at the beginning of puberty when the axons of neurons seem to be reinforced with myelin, even though there is no change in the volume of the brain tissue [9]. Myelin accelerates the transmission of electrical impulses, thus enhancing synaptogenesis, particularly in the frontal lobes [9, 10]. What adolescents would need to be taught at school is how to develop meta-cognitive skills, in order to reflect on the way they learn, and how to objectively analyze and evaluate knowledge in order to form judgments [9]. With regard to the adult brain, knowledge and expertise are heavily depended upon experience. Throughout the lifespan, cognitive abilities reshape the mind architecture by means of development, adaptive abilities, and functioning [9, 15], materializing thus the life-long learning concept. When compared to young brains, elderly brains have been shown to successfully perform cognitive tasks and to reach ceiling scores as the matched young brains, the difference being in the length of the time required for this attainment, due to cognitive control decline [16]. The effects of cognitive functioning and specialization on human brain can be striking. Brain plasticity has additionally been proved to assume a protective role against neurodegenerative diseases, such as Alzheimer's disease, considering that it preserves cognitive functions [15].

What further conditions the classroom synthesis is learner differences. Learner aptitude, learning styles, and knowledge level are factors that a teacher should be aware of before even entering the classroom [8]. Appropriate evaluation and assessment of these facts will enable the educator to better select and design class methodology, in order to render the learning process effective. However, there is yet another parameter too substantial to be disregarded: individual variations, i.e. the uniqueness of individual brain functioning [8, 17]. According to Gardner [17], Western educational systems have been focusing on the cultivation of linguistic and logical-mathematical

intelligences of learners, ignoring and probably creating discomfort to students who best learn through different pathways, hence the term 'multiple intelligences'. Goleman [as cited in 2] also suggested that cognitive skills cannot solely account for a person's successful school life and introduced the notion of 'emotional intelligence', i.e. the ability to monitor, identify, comprehend, and employ emotions as behaviour guidance.

Throughout schooling, learners will have to learn how they best learn, how they acquire new information, and how they can preserve it so that they can retrieve it almost automatically when asked to [18]. Because of the systematic training, constant exposure to knowledge, and repetition, academic performance is expected to excel, unless congenital factors prevent it, as in the case of specific reading difficulties, i.e. dyslexia. Developmental dyslexia is usually associated with failing to acquire alphabetic skills [19, 20]. It is an unexpected reading difficulty, which affects young children and adults. Because it is usually not predicted by lack of intelligence, lack of willingness to learn [20], poor education, or abnormal developmental environment [21], it becomes salient when children are immersed in typical schooling and often co-occurs with deficits in attention and memory, indispensable features for an exceptionally good academic performance.

Visual imagery, imitation, brain exercise, and learning while sleeping have been reported as being successful methods of learning [9]. Yet, no method of learning produces tangible outcomes without motivation, a fundamental component of a learner's profile [22, 23]. It is the desire, the willingness, the enthusiasm to work towards a goal, it is the determination that this goal can and will be achieved. This drive which urges learners forward to reach their object of knowledge can be of an external or internal nature, depending on who or what triggers it. Punishment and reward, along with social and cultural factors, are bound to influence a learner's behaviour and attitude to learning. On the other hand, the fulfillment of internal needs and desires can greatly motivate a pupil. Undoubtedly, the teacher is the decisive person whose leverage will or will not incite and inspire a student to experiment with knowledge. Moreover, the methodology employed in the classroom can further encourage or discourage the continuance of student motivation [8]. The proximity of goal setting to the individual learners' needs along with their continuing adaptation, the physical learning environment and the emotional atmosphere of a classroom, as well as the intriguing, challenging, and purposeful lesson delivery may exert a powerful effect on the initial and continuing motivation of learners [8].

In the classroom

Learning usually connotes classroom [8], as this is the typical education setting which provides students a long-lasting experience of learning within a group of peers, occurring simultaneously with their physical, intellectual, emotional, and social growth [24]. The classroom is a living organism, subject to changes and sensitive to numberless variables which reshape it continually. This is the reason why it is more often than not conjured up as a miniature society whereby a complex network of relationships between the teacher and the students, and among the students gradually develops and bears social characteristics [5]. Students enter the officially implemented framework of education equipped with certain knowledge and skills, depending on their background [25]. Nature and nurture, cognitive, affective, neuropsychological [4], and environmental factors are bound to differentially modulate the approach to novel knowledge within this protected environment. Each and every learner, following diverse ways, is going to explore the paths leading to personal, social, and emotional development, among other areas of learning, including communication, literacy, numeracy, cultural literacy, personal and social skills, values and ethics, self-awareness, and meta-cognitive skills [22, 24].

Being an inherent constituent part of the educational setting, the learner will dramatically affect it, through the constant interference of their evolving personality and temperament. Students experience regular emotional fluctuations while in the classroom, ranging from positive to negative and from activating to deactivating feelings: enjoyment, hope, and pride often co-occur with anger, anxiety, and shame, along with relief, hopelessness, and boredom [26]. Pupils tend to express their fearfulness or excitement in diverse, or considerably extreme, ways [3], which may easily disturb the classroom. This is due to the fact that emotions elicit specific responses to what has been perceived as challenge or opportunity, and trigger behavioural, experiential, and physiological reactions [27]. Schooling years coincide with an often chaotic transition from early childhood through to adolescence. Yet, academic progress is expected to be observed either generally or in a specific learning field. Students are required to provide tangible evidence of their acquired competences through demanding and multiple cognitive tasks. They further need to demonstrate their curricular attainment and steady rate of progress, both at a personal level and when compared to their peers. Apart from cognitive development, it is also imperative that students display self-awareness skills and appropriate social behaviour [24].

In order to understand the world around them and cultivate self-understanding, both teachers and students should learn to attend to emotion processes, identify their emotional status, express their emotions both verbally and by means of extra-linguistic features, and ultimately master emotion regulation [23, 28]. Through social and emotional learning, pupils can learn how to recognize and identify their emotions, control their impulsive behaviour, pursuit motivation, empathize with others, and manage their feelings [2] with the purpose of functioning in harmony with their peers, and optimizing their learning prospects. They can, thus, control their temperament and behaviour, which favours the maintenance of social bonds with their peers and their teacher. By implication, students will be able to function better within the school framework, while teachers will be benefited from the positive conditions in the classroom in terms of delivering their lesson in a non-threatening environment [28]. When the education setting is based on the concepts of respect, supportiveness, opportunity for self-disclosure, productive interaction, and effective communication behaviour, students can be orientated towards healthier ways of emotion regulation[23,28].

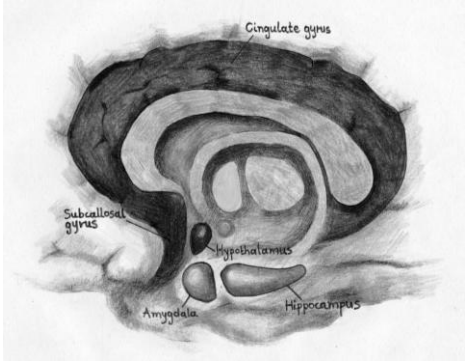
"Man is by nature a social animal; an individual who is unsocial naturally and not accidentally is either beneath our notice or more than human" to quote Aristotle. The sense of belonging and affiliation is an intrinsic human need. The premises of a school and of a classroom in particular can be very decisive as regards the opportunity to freely express oneself within a protected social network. Apart from discovering a broad spectrum of emotions, the students can have the chance to contribute to the learning process with their opinions and to creatively work with their peers. If the teacher aims at establishing a rapport on a very human level with their students, they need to place emphasis on the flexibility of the teaching-learning process in order to respond to the needs and real-time situation of their learners. Urging the pupils to share their experiences enhances their emotional intelligence, inner dialogue, and communication skills. Through such processes, the traditional roles of teacher and student, the former being the possessor of knowledge, the latter being the receiver of knowledge, are challenged. When the trainer and the trainee co-evolve, the educators design the next steps following the evaluation of the feedback they have received, while the learners become responsible for their own evolution, having the educator as their mentor and role model. The encouragement of teacher and student autonomy is further improved if the unique traits of each learner are employed as a means to enrich the teacher-learner relationship, rendering it more mature. Because the learning process is interwoven with making mistakes and misbehaving, it is of paramount importance for the teacher to strengthen the positive educational and behavioural aspects of their learners as opposed to their negative ones.

Nonetheless, the educational environment is not often the place where learning unimpededly occurs, nor is it a place where culture, civility, and respect are promoted. When thoughtless negative actions occur, when there are fights and confrontations, when the rules or procedures are disregarded, then the learners are unprotected against stress or even fear, which are major inhibitors to learning [29]. As mentioned above, the education system is a threefold one, whose constituent parts are the educator, the students, and the parents. Each member of this network is in a position of potentially initiating and sustaining stressful or even fearful feelings to the other two parties. However, it is usually the student who is victimized either by the teacher or by other peers. The latter case has been tormenting the life of students for at least 30 years to the detriment of their academic performance not to mention the irreversible, traumatic effects on their physical and mental health as well as their longevity [29, 30].

The phenomenon of peer victimization, commonly referred to as bullying, has unfortunately become a commonplace in contemporary educational settings. The intimidation several students experience because of the inappropriate behaviour of their peers towards them confirms neuroscientific findings on the consequences of stress or fear on human nature. School teachers report the gradual decline of either high- or low-achieving students, who display a learning profile comparable to students with special educational needs. Intimidated learners develop and ultimately express fear towards school attendance and participation in school activities, particularly excursions, their responses to learning are compromised, their social judgment becomes blurred, their cognitive performance deteriorates, and their self-esteem dims [31]. Coupled with the fragile psychology which leads to symptoms of depression that such students usually present with [31], school intimidation could potentially lead them to desperate ventures [30]. Peer victimization can be of various sorts but the main categories which have been discerned are physical, verbal, and cyber bullying [30]. What tortures the victims of bullying is not so much the physical pain – if any – but rather the inflicted social pain, which is related to social exclusion and rejection [29, 32]. Recent discoveries [32] have suggested that even though the physical pain can be transient and leave its mark in memory as an unpleasant experience, people will long suffer from social pain because it can be easily re-lived and re-experienced. The main reason for this concordance between the two aspects of pain is that both share the same brain region [32].

Unquestionably, students should learn that they are capable of empathizing with other people, of understanding and sharing their feelings. The role of empathy is critical in the development of social interaction between or among people, especially within the classroom, considering the complexity of the emotional networks and their interdependence. Empathy among students can become a critical precursor of the creation of the best possible learning environment, a major concern to a teacher [9]. In order understand how other people feel, a certain process is apparently triggered whereby action mimicry shapes our emotional state; this is feasible because the insula transmits representation stimuli to the limbic areas of the brain [33].

The emotional brain



The brain is a multi-faceted organ with infinite potential and unexplored areas, functioning in a complex, plastic, dynamic manner and carrying out unique neural computations [18]. The part of the brain initially referred to as the limbic lobe or the emotional brain is the locus of an array of emotions, namely of anger, fear, pleasure, sadness, joy, sociability, and sexuality [34]. More recent research has confirmed that this region is involved in emotional processing [6, 18, 33, 35-37], learning, and memory, though the emotional specialization of the limbic system has not been unanimously accepted [35]. The limbic system comprises limbic structures (the cingulate gyrus, corpus callosum, and parahippocampal gyrus) which connect with each other and other subcortical structures (such as the amygdala, hypothalamus, thalamus, and basal ganglia) [18]. The emotional networks of the human brain, as they have been studied by

scientists over the last decades, are the result of the evolution of the primitive cortices [18, 34] whose aim was to alert the brain and respond immediately to imminent dangers [29, 34, 38]. In fact, the limbic system is phylogenetically older than adjacent areas [18, 34]. In concert, animal studies focusing on the feeling of fear have shown that the emotional patterns which the animals displayed when presented to stressors were similar to human reactions [38]. In order for both animals and humans to adapt, survive, and protect themselves in a hostile environment, a defense system [18, 34, 38] has been developed and evolved within the temporal lobe [7, 18, 35-38]. When animals and people are in danger, they react in analogous terms: they are rendered inoperative, their heart rate augments, stress hormones are released [7, 18, 38]. Because both fear and anxiety are powerful enough so as to account for physiological responses with or without conscious assessment of the stressor(s), scientists are optimistic in that the animal experiments reflect the human reaction pathway rather faithfully [18, 38]. However, what differentiates the experience of fear and emotions in general between animals and humans is cognition and consciousness [18], i.e. the ability of the human brain to verbalize, reflect upon, identify emotions, and ultimately understand emotional reaction [18]. The absence of such ability, along with other characteristics, leads to difficulties in emotional regulation, otherwise termed 'alexithymia' [39].

Emotionally arousing stimuli may be of explicit nature and have various forms, i.e. sounds, visual inputs, and language prompts, in which case they induce the arousal of fear; conversely, such stimuli may be implicit, and need not be cognitively processed, mobilizing thus the arousal of anxiety [38]. When an organism is physically or psychologically threatened, or when an organism regards a threat as being a stressor, a basic neuroendocrine system is triggered in order to respond, i.e. the hypothalamic-pituitary-adrenal (HPA) axis [31, 40]. The ultimate chain effect of this modulation is the secretion of glucocorticoids (i.e. cortisol) [29, 37, 40]. The main function of the glucocorticoids is to increase the energy readiness of various systems throughout the organism, in order to better respond to the perceived changing environment [40]. This leads to psychophysiological manifestations and knowledge retrieval which are similar across age and species [18, 38, 40, 41]. However, the prolonged activation of the HPA axis due to heightened emotional arousal can have detrimental effects on the health of the organism across various levels, such as memory impairment [31, 40, 42]. Conversely, if the perceived stimulus is neutral, then the secretion of cortisol may improve memory function [42]. Elevated symptoms of depression, as a result of excessive exposure to acute threat, induced HPA dysfunctioning, which in turn triggered hippocampal neurotoxicity, hence memory deficits [31]. Accordingly, in the case of peer victimization, the victims of bullying stand seemingly defenseless against their victimizers and cannot merely escape the imminent danger because of the reduced cortisol secretion [29]. The acuteness of the experienced stress, the recurrent abuse, along with the prolonged exposure to the stressor hampers their neuroendocrinology [5, 7, 29, 31], with further implications for their cognitive and social skills [5, 7, 29, 31]. The effects of school intimidation may ultimately disturb normal biological functioning since they interfere with the DNA phenotypes [29].

Another effect of elevated cortisol has been seen in the hippocampus, which is particularly vulnerable to corticosteroids [37]. The hippocampus is the locus of a dense network of glucocorticoid receptors [12]. When exposure to stressors is prolonged, then its functions can be irrevocably hampered [37], because its major intrinsic connections are unidirectional [18]. The integrity of the hippocampus is associated with learning and memory tasks [18, 40]. Its increased activation during the encoding of novel events [18] is particularly interesting for learning purposes, considering that learners' motivation is constantly fuelled when introduced to novelty. As to memory, although the hippocampus plays a time-limited role in memory consolidation [12], it does not store long-term memories [12, 18]. Instead, it receives sensory input from other brain regions and forms vague representations of perceived experiences, while it seemingly facilitates the (re)organization of the information to be consolidated [18]. Of equal importance as to contribution to memory processing is the parahippocampal gyrus, because it provides the hippocampal region with input [14]. The susceptibility of the hippocampus to cortisol exerts deleterious effects to its neurogenesis and neural viability, while explicit memory, a crucial hippocampus-related cognitive function, might also be impaired [37]. Explicit or declarative memory is connected to conscious knowledge an individual possesses and is located in the medial temporal lobe [18, 35]. One of the most important structures of the limbic system1, the amygdala, is implicated in the detection of stressful events and initiation of a response to them [29, 43]. The basolateral region of the amygdala plays a key role in the transmission of auditory information to the central nucleus [36, 38, 43]. This nucleus receives sensory information and mediates behavioural and physiological effects to the central nucleus of the amygdala as response to the stressors [43]. Furthermore, the basolateral nucleus of the amygdala mediates memory consolidation in other brain regions [12]. The central nucleus of the amygdala seems to be processing the conditioned fear response [18]. It receives external or internal signals which subsequently target various hypothalamic and brainstem areas [38]. Each target area then triggers differential behavioural responses and generates distinctive signs of fear or anxiety [38], hence fortifying the defense system. Anxiety seems to be processed by the bed nucleus of the stria terminalis, which, together with the central nucleus of the amygdala modulate emotionally charged stimuli [38]. LeDoux and partners [36] suggested that if the acoustic information the amygdala receives is affectively charged, it may modulate the emotion of fear [38]. In order for the limbic system to respond to fear, apart from perceiving the stressor as a stimulus, it needs to be able to recognize it, which is another attribute of the amygdala [41]. Adolphs and partners [41] demonstrated that patients with bilateral amygdala damage were unable to identify the emotions presented to them by means of facial expressions. These

Figure 1. The limbic system – right hemisphere view. Drawing by artist Nikos Podias (2015).

patients, because of the lesioned amygdala, could not draw on previous knowledge and experience which associates specific facial expressions with specific emotions.

Because the amygdala is crucial in fear learning, its smooth function is considered critical in learning in general, due to the adjustability of its mental capacity to retain and revive facts, events, and impressions [35]. The amygdala is indirectly associated with working memory, through the anterior cingulate cortex and the orbital cortex [35]. Working memory is a critical workspace which contains information that can be retained for a limited time in order for mental operations to be performed [18, 35]. The input working memory receives may originate from either sensory memory or long-term memory [18]. Research has shown that working memory enables the reception of a wider spectrum of stimuli, when these are affectively charged [35], which underscores the importance of the amygdala in the learning process. Interestingly, Erk et al. [14] showed that activation in the amygdala region was a precursor for later successful memory, when it was delivered within a negatively charged context. However, when the stimuli were presented in a positive context, it was the activation in the right anterior parahippocampal and fusiform gyri which predicted subsequent successful recall [14].

Along the same line, Sapolsky [37] reports research which has shown that exposure to mild or transient stressors can favour implicit memory. Implicit or nondeclarative memory is connected with unconscious knowledge and functions in a learned and autonomous way [18, 37]. In these instances of fear it is the amygdala which is directly affected, because in the event of prolonged exposure to stress, amygdala-related cognitive functions are facilitated and experiential memory is intensified [7]. Even though this might seem quite remarkable, and even from a cytoarchitectural perspective the amygdala is enhanced, it should be noted that stress has ultimately detrimental results to both the hippocampus and the amygdala [37]. Erk et al. [14] ponder over the lateralization of the amygdala activation during emotional arousal. The amygdala lateralization issue was also reported by Hölzel and colleagues [43]. Wishing to observe whether there can be a bidirectional correlation between amygdaloid gray matter density and perceived stress reduction, they trained healthy individuals in a mindfulness-based stress reduction intervention. The results corroborated the experimental hypothesis and showed decreases in the right basolateral amygdala grey matter [43].

Neuroscience + Pedagogy = …

The microcosm of a classroom is a potentially fertile ground for the findings of neuroscience to be applied in order for real-life incidents to be accounted for. Indeed, what a teacher observes as poor performance of a student might be the joint product of a series of reasons pertaining to attentional systems, synaptic connections, even genes [44]. To this end, both educators and neuroscientists could exchange experiences and experimental findings with the ultimate purpose of improving educational curricula and adding a real-world perspective to neuroscience. Were this coalition be fostered, the in vitro outcomes could be validated or disproved when projected or tested in vivo. Neuroscientific research, though promising, has not as yet become an applied science with regard the improvement of the actual classroom setting, both in theory and in practice [9, 23, 45, 46]. One possible explanation could be the lack of mutual assistance between the two disciplines [23, 46]. Even though the two fields could inform each other and orientate research towards new experimental horizons, this converging point seems difficult to attain. If neuroscience is solely viewed as a descriptive discipline, whose main concern is the exemplification of factual truth, while education is only considered as an intervention discipline, whose aim is the assessment of methodological efficiency, then it is only through purposeful communication that this epistemological gap can be bridged [23]. In fact, cognitive neuroscience could certainly provide guidelines and suggest practical solutions which could result in reformed teaching methodologies and teaching tools [23]. Research conducted so far within the fields of educational and instructional science, cognitive developmental psychology, and information technology have been informing learning sciences with empirical evidence about how learning is mastered, what the learning profiles of learners are expected to be, how critical the environment of a learner is to their academic performance, what methodologies have been deployed, whether they have helped the learners to improve, what the underpinnings of academic failure are, where the new trends in teaching and learning point at [45, 46]. Obviously, these scientific findings should not be undermined; rather, they should be enriched. The exemplification of the potential strengths and weaknesses of the learning brain with precise and applicable suggestions for the classroom would be a true future challenge [46].

= 'Neuropedagogy' …

The creation of a new comprehensive, transdisciplinary, conceptual field, encompassing biology, cognitive science, development, and education has received much attention recently, and has been termed in the literature as mind, brain and education (MBE) [10, 44, 47]. The scope of MBE is to function as a mediator between teaching and learning researchers on the one hand and educationalists on the other hand in order to reshape education by means of enhancing educational materials and suggesting reforms to education stakeholders and policy makers [44, 47, 48]. An educational setting does not necessarily entail a classroom alone; playing fields, television, the Internet, the media, peer and family interactions and experiences can equally shape the teaching-learning process and education research should include those settings as well [23, 47]. The MBE researchers posit the role of biology in the advancement of educational research by means of perceiving the learning pathways along with the range of abilities and disabilities that may occur during the learning process [10, 47]. From a biological perspective, learning occurs because the brain, being a receptor sensitive to environmental messages, responds to the

internally generated stimuli which are shaped by the externally triggered concepts of education [10]. As a result, the neuronal connections are strengthened in order to store information and the whole brain architecture adapts to the new inputs through the formation and reformation of neuronal circuits [10]. Bearing these brain features in mind, instruction methodology can be designed in a more biology-wise sense, following the pace of brain evolution throughout the lifespan, without neglecting the effective role of emotions to learning [49].

In order for a bridge between biology and education [11] to be built, a threefold scientific foundation is necessary: real-life research schools, where research questions and methods can be directly implemented as a result of a productive collaboration between researchers and educationalists; databases on learning and development, which will collect data from real-life educational settings and assess evidence-based practices; educational translators or engineers, who will actually implement the research findings in the classroom in order to test their validity and efficiency [23, 47, 50]. Accordingly, Gardner [50] coined the term 'neuroeducator' to suggest the professional whose responsibility would be to evaluate research findings, decide on courses of action based on empirical results, and recommend policies. Through this careful design of educational practices, teachers and learners will become more autonomous and efficient towards the achievement of their goals. Teachers would be given alternative ways to differentiate their teaching in order to accommodate the needs of most of their pupils [49]. As far as the educators' opinion on the role of neuroscience in education, the findings of a relevant study showed that educators appreciate the inextricable involvement of the brain in various aspects of teaching and learning methods [51]. However, what teachers reported as crucial, before fostering any relationship between education and neuroscience, was the simplification of the communication code between the two disciplines [51], a remark later corroborated by the MBE researchers [48].

… or 'Emopedagogy'?

On the other hand, there seems to be a need for neuroscience to explicate the concepts of social cognition and emotional regulation and suggest plausible implications for pedagogy [45]. The way students feel towards education, learning, schooling, and their teachers is certain to affect their behaviour as learners along with their cognitive learning, i.e. the mastering, employment, and understanding of knowledge [52], and state motivation [53]. More specifically, the students who regard school as a pleasurable way of approaching knowledge are expected to comply with the tasks their role entails. The more this pleasure is strengthened, the more pleasurable school becomes. These positive feelings can be further intensified within a classroom where a student feels confident enough to master novel knowledge and accomplish their tasks. Pleasure-displeasure, arousal–non-arousal, and dominance-submissiveness are the three dimensions along a continuum of emotional responses a student experiences while in the classroom, according to the emotional response theory (ERT) [54]. This theoretical model sought to explicate the nature of interactions among the behavioural, affective, and cognitive traits of a classroom, by examining the causal effects of teacher behaviours onto the students' feelings, and ultimately onto the learning outcomes [26, 53-55]. Although this theory has been empirically substantiated, some of the causal relationships ERT posits between the emotional responses of the students and the instructor behaviours have been challenged by researchers [53, 55].

According to ERT, teacher nonverbal immediacy, teacher communication competence, and teacher clarity may arouse a range of emotions in students [54, 55]. An immediate teacher is "... a teacher who seems relaxed, animated and vocally expressive during class lectures and discussions, moreover, this teacher smiles frequently, engages in a lot of eye contact and is generally perceived as friendly and approachable." [52]. It seems that an immediate teacher may exert a powerful effect on the students' tendency to resist compliance with their tasks [52]. Instructor immediacy positively influences the learners' cognitive and affective learning, i.e. their standpoint with regard an issue or a person [52, 54]. It would equally be interesting for researchers to examine the impact of teacher immediacy on the physiology of the learners with respect to all emotional responses they experience while in the classroom, along the relevant continuum suggested by ERT [53]. Classroom management is further favoured be teacher immediacy, since student achievement will have been secured while chances for either student resistance and/or misbehavior will have been diminished [52]. Moreover, the way a teacher communicates with their students may moderate student emotional responses [53]. This conclusion pertains to the concept of teacher communication competency [55]. Teacher communication competency refers to the appropriateness of communication behaviours of teachers within the classroom setting [56]. The third pivotal notion suggested by ERT, namely teacher clarity, alludes to the ability of the teacher to present novel material in an understandable, illustrative way which respects the students' rhythm of understanding and their need for abundant practice [57].

Apparently, an immediate, communicatively competent, and clear teacher is going to foster a solid relationship with the students, which will be endowed with emotional support. When the students receive supportive messages from their teacher, their stress and anxiety can be alleviated, they can deal with the learning objective more effectively, their emotional health is safeguarded, and their inter-personal expertise is promoted [58]. On the contrary, a nonimmediate, communicatively incompetent, and unclear teacher is going to intensify negative and deactivating emotions in the students, which will induce harmful chain effects [26]. Anger, anxiety, shame, hopelessness, and boredom [26] are bound to emerge causing the teacher-learner bond to dissolve. However, it should be borne in mind that when a teacher walks into the classroom, they are already emotionally laden. Self-perceptions, previous experiences with, emotions towards, and emotions perceived by a specific class are going to greatly influence the affective communication with those students during that lesson, while reshaping the social dynamics network of the whole classroom.

Discussion

The aim of this paper was to demonstrate basic features of what constitutes a classroom setting, in terms of the people involved, how they function with respect to education and learning, and what contemporary trends suggest with respect to the enhancement of the teaching-learning process. Learning presents with a twofold expression, namely cognitive and emotional competency. It is the latter that needs to be more fully addressed, considering that nature and nurture, cognitive, affective, and environmental factors are interwoven during the schooling years of a person's life. Considering that school constitutes a comprehensive social environment, emotional competency allows learners to meet its requirements and shapes their personality and temperament. Cognitive neuroscience methods have provided an explicit locus of the affective part of the brain, i.e. the limbic system, and have shed light on the functioning of the amygdala and the hippocampus. Stress or fear may hamper the connections of this part of the brain with the frontal cortex thus compromising responses to learning, social judgment, and cognitive performance. A type of chain effect is created emerging from stressful feelings in the classroom, which disturb the attention skills balance, hence affecting learning capacity. Emotional processing seemingly regulates educational processing and accounts for the different reactions of the learners to new educational situations.

Being an educator at a special needs secondary school has incited me into attempting this small-scale theoretical research into the field of emotions in connection with the brain. My main incentive was to learn, probably because I have been infused with the concept that a teacher cannot teach unless they learn. Perhaps this explains the constant need of educators to update their knowledge, their teaching techniques and learning tools. They are usually eager to be educated by experts of various fields in order to feel even more adept at facing the challenges of the next day at school. However, the classroom reality can be dramatically different from what researchers might consider it to be. Using the example of intra-classroom variations of a special needs school, the tasks a teacher is required to accomplish seem unreal. The actual subject of instruction might become secondary because effective and efficient classroom management is the primary concern of the teacher. The differential deficiencies of students, each of which requires individual educational plans and almost always individualized behaviour, create a very peculiar classroom setting, where the network of relationships between the teacher and the students, and among the students is utterly fragile. Stress, anxiety, fear, shame, boredom, and hopelessness are equally shared by teachers and students. Only, they derive mainly from the nature of the disorder each learner has been diagnosed with and the additional emotional load on behalf of the educators. Which novel scientific field could suggest an educational program that would accommodate the needs of a classroom where students with intellectual disabilities co-exist with students with pragmatic communication disorder, autism spectrum disorder, disruptive mood dysregulation disorder, and non-suicidal self-injury disorder? How can teachers safeguard their cognitive and emotional health when they move to another classroom whose synthesis bears no similarity to the previous or the following one?

Experience and practice has shown that establishing a rapport with the students can facilitate the classroom climate and subsequently the teaching-learning process. Good behaviour, self-discipline, and respect, along with responsibility, and cooperativeness may be the recourse for both the educator and the learners to gradually grow immune to awkward and threatening situations. Rewards and sanctions are to be seriously reflected on since they contribute to the improvement of the quality of student behaviour and trigger their motivation. However, in the event of unacceptable behaviour, or breaking the school rules, or failure to follow reasonable instructions, it is the teacher's duty to discipline the misbehaving student, as a means of socially educating the whole class. It is then that the task of being in a classroom becomes purposeful, because the learner is treated as a whole person, who is guided to develop multiple skills in the cognitive, affective, and moral domains. On the other hand, the teachers, in spite of the adversities, are in the proud position to enlighten their learners and generously share with them the treasures of knowledge.

"I am indebted to my father for living, but to my teacher for living well." (Alexander the Great)

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Multimodal sensing and fusion for comprehensive monitoring and feedback: the integrated Dem@Care system

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Abstract

The widespread prevalence of dementia and its co-morbidities, combined with the increasing age of the worldwide population and the subsequently decreasing care ratio, have motivated the development of solutions for more effective remote monitoring and care. Dementia affects many people worldwide, who gradually become unable to continue living independently and require help from formal (doctor, nurse) and informal (family, friends) carers. The social and economic costs of this condition are great, affecting individuals, societies, healthcare systems and the workforce among others. The Dem@Care project proposed a multi-sensing solution for the remote care of people with dementia. The multi-sensor outputs are intelligently fused to provide relevant, personalized care options, helping clinicians and informal caregivers (e.g. nurses, family members) provide better feedback and the individuals take better care of themselves.

Introduction

Dem@Care aims to assist clinicians with earlier and more accurate disease diagnosis by enhancing existing examination protocols with multi-sensor monitoring outcomes that provide a comprehensive picture of the person's condition. Its ultimate goal is to help people at early stages of dementia receive personalized remote care and support them in their daily life, allowing them to retain their independence for a longer period of time. Thus, within Dem@Care a multi-sensing platform has been developed, where the sensor measurements are intelligently fused to provide relevant, personalized high-level descriptions of the person's condition and its evolution over time. It involves two closed loops, one between the person with dementia and their formal caregivers (clinicians), and one between the person with dementia and their informal caregivers (e.g. relatives), shown in Figure 1.

Figure 1

Figure 1: Dem@Care closed loops for the patient and the clinician. Multi-sensor measurements are fused to provide a high-level assessment of the person's health status and provide relevant care options such as lifestyle modifications.

In the Dem@Care context, the person with dementia carries out daily activities, either at home, or in controlled conditions in a hospital lab environment, which are measured using multiple sensors, whose outputs are fused intelligently to form a clear picture of the person's condition and lifestyle. This will facilitate the development of targeted, personalized remote care solutions, feedback and support. Changes in the person's condition and lifestyle (e.g. sleep problems) will be detected in a timely manner, allowing for rapid intervention if needed.

The measurements lead to feedback for the people with dementia, tailored to their individual needs and aiming to be as discreet, simple and easy to understand as possible. More detailed in-depth descriptions of the person's condition are provided to the clinicians, allowing them to better understand the person's status [1] based on objective, daily measurements, as opposed to currently used periodic questionnaire-based assessments, which are often subjective and are therefore unreliable in some cases. This comprehensive picture of the person's condition and its evolution helps them provide relevant and necessary care solutions and feedback, such as advice on lifestyle improvements or reminders. The continued monitoring also allows for the evaluation of the proposed care solutions (such as lifestyle modifications) and the detection of changes in the person's condition.

Dem@Care Sensing Solutions

The sensing solutions in Dem@Care are chosen based on clinical expertise, aiming to provide the most relevant and reliable description of the person's condition, while at the same time remaining unobtrusive and low cost, to ensure future adherence. Clinical partners in the Dem@Care project indicated five areas of interest for monitoring individuals with dementia: social activity, sleep, physical activity, execution of Activities of Daily Living (ADLs), mood. These areas indicate the person's capability to live independently (e.g. by successfully carrying out ADLs, sleeping regularly without interruptions), and their overall physical and emotional condition. For example, a decrease in social activity or worsening of their mood may indicate a deterioration of their condition. Multiple sensing solutions exist and have been deployed for the assessment and monitoring of these areas, with some sensors providing complementary information about a particular area of interest. For example, activity levels can be monitored via visual sensors and accelerometers, so their fused outcomes provide a robust indicator of a person's level of activity and how it changes over time. This provides an indirect indication of the person's emotional status, who may decrease their activities if their mood declines, which can also be assessed from speech analysis [2,3]. Thus, the fusion of such measurements is expected to give a richer, more robust and accurate depiction of the person's status.

Overall, the sensing modalities can be divided into two types: ambient and wearable. Ambient monitoring will include monitoring of their environment, utility usage (via contact/motion sensors, smart plugs), sleep monitoring, and ambient visual sensing for detecting activities of daily living [4], levels of activity and sociability, behavioral and lifestyle profiling and monitoring. Wearable sensors will be used to monitor health parameters, voice [5], emotional and cognitive status, while wearable visual monitoring will provide a detailed and refined view of daily activities [6]. The ambient visual sensing involves the detection and recognition of ADLs [7,8] in an unobtrusive manner, to assess the person's lifestyle and behavioral patterns and detect changes in them. Wearable visual sensing is used for accurate spatial localization of the individual in the scene and object recognition, which subsequently lead to more accurate and detailed activity recognition [9,10]. The table below shows the wearable and ambient sensors used in Dem@Care and their use.

Dem@Care Intelligent Fusion for Decision Support

The variety of sensors employed within the Dem@Care system provide multifaceted information that varies from person-specific captured data (such as vocal attributes) to information related to the actions, such as eating, performed by the person with dementia (PwD), and the environment of the PwD (such as objects the PwD interacts with). Though each one is informative on specific aspects of interest, the individual pieces of information are not capable of delineating the situations in which the PwD may be involved. Combined pieces of information on the other hand can plausibly represent the behavior of the PwD and explain incurring situations.

In Dem@Care, state of the art sensor fusion technologies [11 are used for aggregating individual pieces of information and meaningfully fuse them in order to derive high-level interpretations of the PwD behavior, easily used by caregivers and even the patients themselves. For example, clinicians can obtain a detailed picture of the person's sleeping patterns and how they change over time, also in relation to the person's other activities. On the other hand, patient feedback may only provide reminders to the person, or advice related to lifestyle improvements (e.g. "you should go outside more often" if they are inactive etc.). Through intelligent fusion and context-aware aggregation of the different types of knowledge, Dem@Care provides personalized feedback and care management services, coupling clinical and domain knowledge with profile contextual history and care plans. The Dem@Care application context involves the detection of:

- atomic activities and measurements by means of monitoring and analysis components (e.g. body temperature, light level), as well as complex activities after intelligent fusion and analysis (e.g. having meal, sleeping, answering the phone, having a face-to-face conversation, etc.)
- problems and situations that the clinicians need to be informed about (e.g. missed meals, excessive napping, insufficient communication attempts, nocturia, etc.)
- clinically relevant attributes and summaries (e.g. sleep efficiency and duration, number of daily telephone and face-to-face interactions, night sleep summaries, etc.).

Dem@Care Feedback

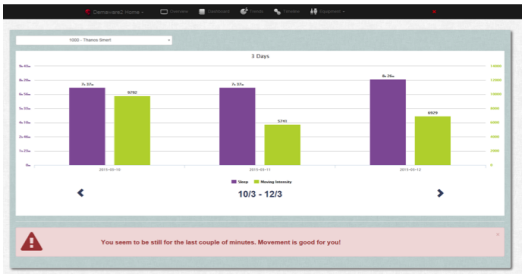
The fused sensor outputs are then sent to the end users, in appropriate interfaces. Patient feedback is very simple, aiming to support them in their daily life, but without providing potentially confusing details. The patient feedback may be only a simple reminder of a doctor's appointment and may be provided only at the patient's request. The feedback to caregivers, especially clinicians, is much more detailed, covering all aspects of the individuals' life on a daily, hourly basis. The feedback can be provided via various devices, namely a smartphone, tablet and also the personal computer of the end user (doctor or PwD).

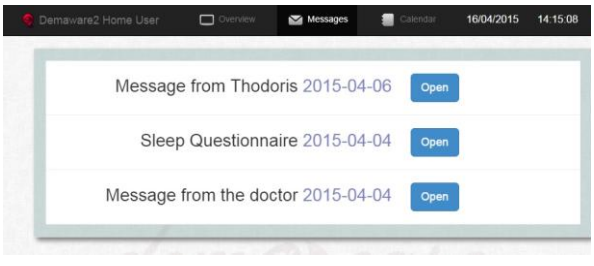
More detailed insights into the person's daily life can be seen in the figures below. In Figure 2 we see a very detailed breakdown of a person's day, according to the various activities they carry out and the precise time instants when they perform them. Figure 2 below shows samples of feedback, for patients from informal caregivers and doctors The clinician's interface can be seen in Figure 3 below, where a high level overview of the patient's daily activities and overall status is also provided in the bottom of the screen. The clinician can zoom in to see more details about any activity of interest or concern.

Ambient Sensors	Use
Color-depth camera (Kinect, Asus RGB-D camera) 	Detection and recognition of ADLs Monitoring of daily life patterns (e.g. execution of ADLs over time) Indirect assessment of a person's independence via their ability to carry out ADLs Indirect assessment of a person's mood and wellbeing
Sleep sensor: Aura, Beddit, Gear4 	Qualitative and quantitative analysis of sleep patterns and quality Detection of interruptions of sleep Correlation of sleep quality with other lifestyle factors such as levels of activity etc.
Motion Sensors	Monitor use of daily living objects (e.g. coffee pot, iron etc) Assessment/logging of daily activities carried out
PIR Sensors (Passive Infra-Red)	Detect presence of people in certain rooms/locations (e.g. bathroom visits)
Smart Plugs 	Utilities usage Monitoring of lifestyle

Wearable Sensors	Use
Wearable GoPro camera 	Location recognition (e.g. room in the house) Object recognition Detailed activity recognition through the incorporation of object information.
Wearable microphone 	Assessment of person's emotional and cognitive status through the analysis of speech (statistically significant correlations can be made between the person's speech and their cognitive status. Indirect assessment of levels of sociability: increased speech with other individuals indicates higher levels of sociability.
Wearable fitness/physiological tracker (e.g. Jawbone, Fitbit etc) 	Assessment of levels and type of activity, e.g. step counting, stairs climbed, calories burned etc. Sleep tracking Physiological measurements used for the assessment of stress e.g. heart rate tracking, skin conductance Fall detection

Σφάλμα! Το αρχείο προέλευσης της αναφοράς δεν βρέθηκε..





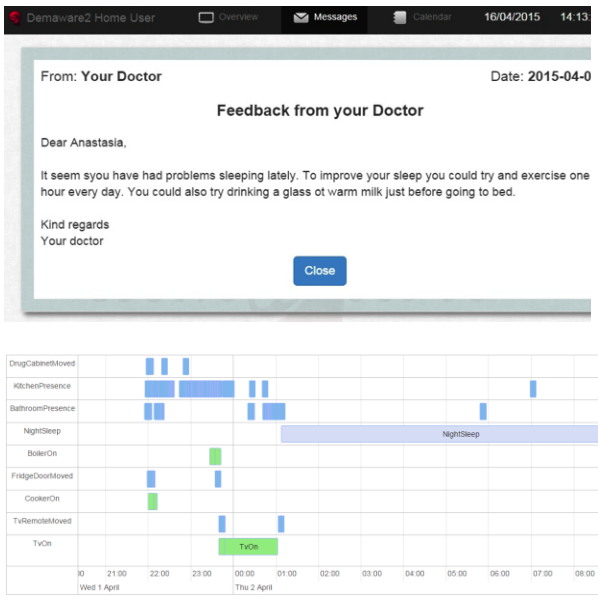


Figure 2 Activities carried out during the day. The clinician can zoom into the time intervals of interest to get a clearer picture of the person's lifestyle

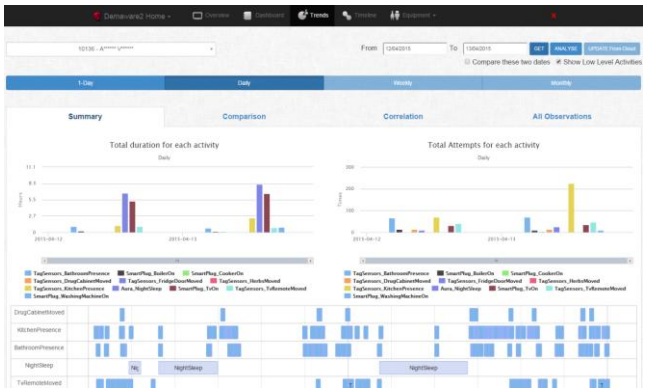


Figure 3 Clinician's interface providing detailed activities and high-level information such as total occurrences and duration of events related to the person's daily life.

Finally, characteristic indications of problems in a person's daily life can also be seen in the Dem@Care interfaces, as in Figure 4 below. We can see when the person's stress levels are elevated, when they had insufficient social interactions and so on, allowing clinicians to draw conclusions about dementia and factors that lead to its worsening or improvement.

Figure 4 Clinician interface showing problems in the daily life of the PwD.

Dem@Care Pilot Testing

The integrated Dem@Care system is tested out in pilots in three locations and three countries. The locations are a hospital lab, a nursing home and peoples' homes, while the countries are Ireland, France and Sweden. Additional measurements took place in the Greek Association for Alzheimer's Disease and Related Disorders (GAADRD) in Thessaloniki, Greece, to enrich the dataset and provide additional benchmark data for training and testing the algorithms developed in the project.

Dem@Lab is applied in hospital lab settings, where the people with dementia are asked to perform a set of semi-supervised activities. In particular, they are given a list of activities, such as "water the plant", "prepare your pills", "make a phone call" and are asked to execute them in the order listed on the paper in a pre-set period of time. Multiple sensors are used during the lab tests, with a static video camera recording the person, a wearable camera recording their activities and the objects they interact with, and a microphone recording their speech. Wearable fitness/physiological sensors measure their physiological characteristics, speed/gait, heart rate etc, which can be used to evaluate their emotional state as well. The objects in the room the person is carrying out the activities are equipped with motion sensors as well [12], to detect when they are used. For example, the motion sensor on the water kettle indicates when the person tries to make a cup of tea.

The deployment of Dem@Care's platform in nursing homes is referred to as Dem@NursingHome [13]. In that case, the platform aims to facilitate the life of individuals in the nursing home as well as their carers. This environment is less constrained than the hospital lab, but more constrained than a person's home. Its most significant focus is on supporting the carers (e.g. nurses) and providing alarms in case of an emergency.

The deployment of Dem@Care in homes, referred to as Dem@Home, is the ultimate test of the system, as these environments are completely unconstrained and different among each other. Pilot testing in homes in Ireland and Greece is taking place, where initial results are already showing improvements in a person's overall condition and a much more detailed and comprehensive picture of their lifestyle, which can provide clinicians with valuable insights and eventually lead to new medical knowledge.

Figure 5 below shows some detailed daily life monitoring outcomes, for example when and how many times TV and cooking device (cooker) were turned on, when the person visits the kitchen/bathroom etc.

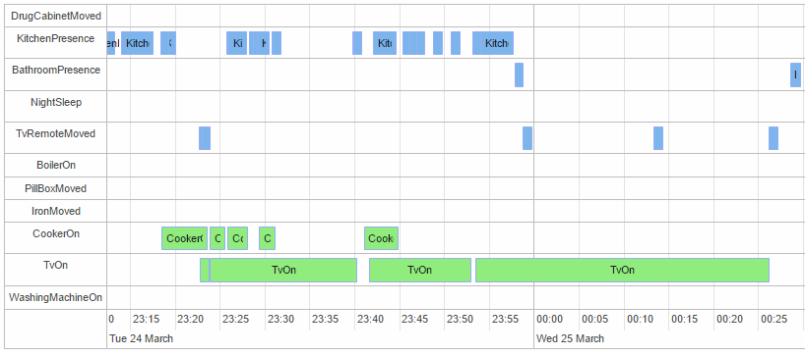


Figure 5 Detailed daily life monitoring: we can see when the person moves the pill box, visits the kitchen/bathroom, opens the refrigerator etc.

An example of sleep monitoring outcomes is seen in Figure 6 below. The time the person spends in bed but remains awake is measured, in addition to the total time the person is asleep, in shallow and/or deep sleep. The number of interruptions during the night is also measured, indicating the quality of sleep.

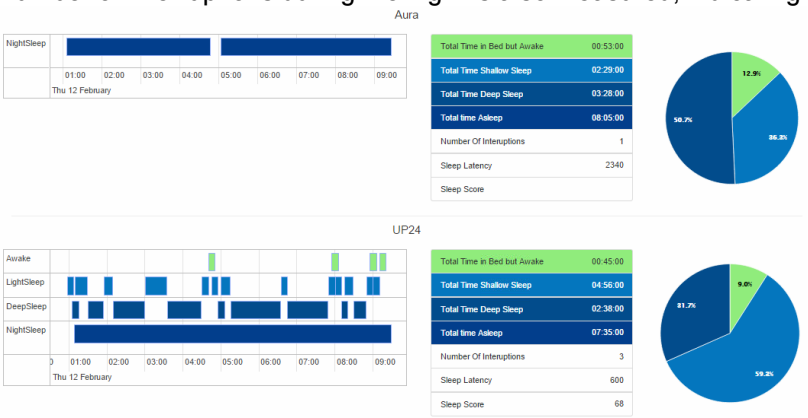
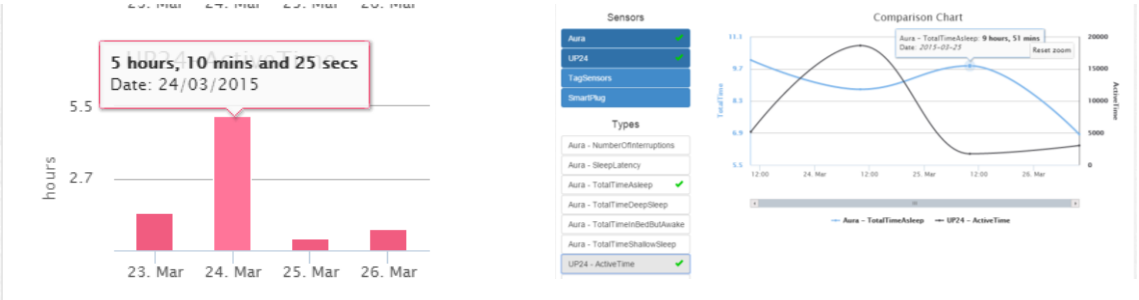


Figure 6 Sleep monitoring outcomes from the deployment of Dem@Care in real homes.



The various sensor measurements are correlated and can provide useful insights on the most appropriate lifestyle choices for the person's quality of life and overall progress. In,Figure 8 it can be seen that a day of high activity was followed by uninterrupted, high quality sleep. Indeed, the wearable motion sensor in this case provides a detailed description of the person's activity levels, while the sleep monitoring indicates that the individual's sleep was greatly improved the night after they were active.

Clinical Interventions in Dem@Care Pilots

During the Dem@Care deployments, the participants receive support from caregivers, such as specialized psychologists and neurologists. Indeed, for Dem@Home in Thessaloniki, Greece, a psychologist visits the individual being monitored on a weekly basis, and discusses with her about her overall condition, emotional status, as well as the usability of Dem@Care. The platform is shown to be unobtrusive, allowing individuals to carry out their daily activities as before, even using some of the wearable sensors. According to the Dem@Care monitoring outputs and the feedback from the individual, the psychologist recommends an appropriate program for the person, chosen from the following:

1. Dance has been proven to enhance demented people's cognitive skills and their mood, especially when used as a therapeutic intervention for depression. Kattenstroth et al., tested cognitive, perceptual and motor performance in two groups of elderly participants who had a long-year record of regular AD or no dancing experience (control group; intervention group) and they found that the AD group had a superior performance in most of the tests investigated [14]. Another study indicates that older adults trained in contemporary dance once a week for 5.7 months improved their switching attention and cognitive flexibility, as revealed by neuropsychological tests [15].
2. Exercise has been proven to be very helpful for many neurodegenerative diseases such as Myasthenia and Parkinson's [16]. People that exercise feel more comfortable about their age and self-esteem. Also, moving intensity and activity can be used to reduce sleeping problems and insomnia. In the Dem@Care home pilots, the individual is asked by the psychologist to run on a treadmill or do some cycling 2-3 times a week. The resulting sensor measurements show a distinct improvement in the individual's sleeping patterns and overall mood.
3. Reminiscence therapy has been defined as ''using the recall of past events; feelings; and thoughts to facilitate pleasure; quality of life; or adaptation to present circumstances'' [17]. A study by Zhou et al. indicates that, after the experimental group received 6 weeks of group reminiscence therapy, negative feelings scores decreased significantly more than control group, while the positive feelings and affect balance scores significantly increased [18]. Such therapeutic solutions are also applied in the Dem@Care home pilots, with very positive feedback from the end users.
4. Prospective memory and Attention Exercises are applied with good results for the cognitive status of dementia patients. Prospective memory refers to memory for future intentions and is a critical predictor of functional capacity in late adulthood. Memory and general cognitive skills are one of the many problems elders face up when they have dementia. Due to the fact that this disease is progressive, cognitive exercises can delay the decline of dementia and make the person feel better about his/her abilities and cognition.
5. Group Psychotherapy and Relaxation Exercises are also used to assist the individuals with dementia, as they have been shown to be useful for people with behavioral problems such as anxiety, depression or domestic problems. In our case group psychotherapy helps our patient to find out that there are many other people who face memory deficits and depressive symptoms. This will release the pessimistic way of thinking.

Dem@Care Conclusions

Dem@Care was motivated by the need of caregivers to have a better picture of the PwD so as to provide more relevant, personalized and consequently effective care. It was also motivated by the need of PwD to retain their independence for a longer period of time. Indeed, the deployments of the Dem@Care platform in hospital labs,

nursing homes and peoples' homes is indeed very promising, improving the quality of life and quality of care for all end users. The detailed, in-depth picture of the person's behavioral and lifestyle patterns provide a much clearer picture of their status, facilitating early detection of warning signs and the provision of optimal, personalized care solutions. Clinicians are able to remotely monitor the person's progress and adherence to treatment protocols, and also evaluate their level of independence. Informal caregivers are alleviated of the burden of daily care, while still being able to monitor the PwD. Finally, the PwD themselves feel an increased sense of safety and support, which improves their overall emotional status and quality of life. Future extensions of the Dem@Care solution include the deployment of the latest monitoring technologies, for an even more unobtrusive solution, and improved feedback to all end-users for optimal usability and therefore adherence.

The authors declare that they have no conflicts of interest.

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The travails of dementia policy development in a small island state: perspectives from Malta

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Keywords: Dementia - Malta – Policy

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Abstract

Malta, the smallest country in the European Union, is experiencing a demographic transition where the share of individuals aged 65-plus currently makes up 16.3% of the total population. This figure is projected to reach 31.2% by 2060. While the opportunity to grow older indicates social success, it creates important challenges at both the personal and political economy levels. As a result of this increase in the number of older persons, age-related neurodegenerative disorders, including the most common forms of dementia, are expected to rise proportionately. This will pose significant societal demands as most dementia care is provided informally by family members living in the community. Furthermore, recent studies have shown that there is considerable lack of awareness and professional training that is seriously undermining timely diagnosis and management. As a result, Malta opted to take a holistic approach towards dementia care by recently launching a long-term strategy focusing on increasing awareness, providing the best services leading to high quality dementia care, and fostering dementia training to healthcare professionals in order to be better equipped to support individuals with dementia. It is a vision that promotes excellence, and effectively reflects the current and future needs of these individuals, their relatives and caregivers.

Introduction

Dementia is a group of brain disorders characterized by progressive deterioration of cognitive function. It is the most common neurological disorder in old age and a major predictor of morbidity and mortality in the elderly. The most common form of dementia is Alzheimer's disease (AD). Other types include vascular dementia, dementia with Lewy bodies, fronto-temporal dementia and dementia secondary to disease [1].

Dementia affects individuals in different ways depending on the type and stage of disease progression [2]. Early-stage dementia is often missed or misdiagnosed due to lack of awareness that often leads to the belief that the observed symptoms are a direct consequence of the normal ageing process. Common signs at this stage include impairment of short-term memory, difficulty in verbal communication and decision making, difficulty in carrying out complex activities of daily living (ADL) and changes in mood and behaviour including depression and anxiety. As the disease progresses to subsequent stages, individuals become more forgetful, have increased difficulty in communication, are unable to perform basic ADL and live independently and may display inappropriate behaviour such as wandering, hallucinations and disinhibition [2]. The amount of informal caring for an individual with dementia is also related to the severity of the condition with half of the caregivers spending more than ten hours a day in caring for an individual with late-stage dementia compared to 20% for early-stage dementia [3]. For most progressive dementias, no cure exists that stops or reverses the observed brain cell death. Treatments available to date are mostly approved for AD and are intended to delay the decline in cognitive symptoms for a limited amount of time [4]. Treatment for the common changes in behaviour depends on the presenting symptoms which vary from one individual to another. These are usually the most challenging and distressing characteristic of the disease process and include agitation, anxiety, verbal and nonverbal aggression, hallucinations, delusions and sleep disturbances [5].

According to Alzheimer's Disease International, the total number of people with dementia worldwide is projected to almost double every twenty years reaching 75.6 million in 2030 and 135.5 million in 2050 [6]. Much of this increase is attributed to low- and middle-income countries, and driven by population growth and demographic ageing [7]. The global societal costs of dementia are enormous as the total estimated worldwide expenditure for the year 2010 was calculated to reach US$604 billion, equivalent to 1% of the world's gross domestic product [8]. The cost of care provided by families (informal care) together with societal care (care provided by professional personnel in home settings) contribute to 42% of the costs worldwide, while direct medical care accounts to 16% of the overall costs. Interestingly, low-income countries account to around 1% of the global dementia costs whereas high-income countries account to 89% [8].

In the recent years, the European Union (EU) has devoted particular attention to the medical, social and financial aspects of dementia. Research on neurodegenerative disorders has been strengthened as part of the Health Theme within FP7 (2007-2013) with special reference to brain research and particular emphasis placed on translational research and the development of new drugs. The Public Health Programme also supported the

European Collaboration on Dementia (EuroCoDe) project coordinated by Alzheimer Europe in order to achieve a comprehensive overview of the present situation in terms of prevalence, diagnosis, treatment, and socio-economic costs of AD in EU-member states. Results from this project indicated that 7.3 million individuals live with dementia in the European Union [9]. In January 2011, the European Parliament adopted a resolution calling for dementia to be made an EU health priority and urging member states to develop dedicated national plans and strategies with the aim of addressing the social and health consequences, as well as services and support for affected individuals and their family members. Taking action against dementia through various intervention streams such as strengthening capacity, leadership, governance, risk reduction, public awareness and facilitating technological and social innovations was one of the main recommendations put forward by the World Health Organization (WHO) in its first Ministerial Conference on Global Action Against Dementia organized at the beginning of 2015. The latter was an aftermath of the progress made since the 2013 G8 Dementia Summit which called WHO and the Organization for Economic Co-operation and Development (OECD) to identify dementia as an increasing threat to global health and support countries to strengthen health and social care systems to improve care and services for people with dementia.

As a consequence of the need to address the challenge of dementia, Malta embarked on a nationwide consultation process, starting in 2009, with the aim of developing a holistic approach towards dementia care through a policy document that focuses on a number of intervention streams including an increase in awareness and understanding of dementia, workforce development, providing the best services leading to high quality dementia care, and fostering dementia training to healthcare professionals in order to be better equipped to support individuals with dementia. The policy document was published and officially launched at the beginning of April 2015 making Malta the 21st country to have a national dementia plan worldwide.

Malta: demography and healthcare system

The Maltese archipelago (315 km²) consists of three main islands: Malta, Gozo and Comino. It is located in the centre of the Mediterranean Sea with Sicily 93 km to the north and northern Africa 288 km to the south. The latest available data show that the total population of Malta in 2013 was estimated at 425,384 of which just over half were females [10].

Malta scores high on the Human Development Index with a life expectancy of 79.2 years for males and 83.6 years for females (Table 1). Circulatory diseases are the leading cause of death accounting to 40% of all deaths followed by 27% for neoplasms [10]. Diabetes is highly prevalent in Malta, a pattern shared with other Mediterranean countries.

Health care in Malta is provided through two systems: statutory and private. Health care in the public sector is highly centralized and regulated. The government delivers primary health care through a number of health centres that offer a full range of preventive, curative and rehabilitative services. In secondary and tertiary care, specialized ambulatory care is provided in public outpatient clinics and health centres. The ministry responsible for health finances, regulates and acts as service provider for public hospitals. A number of private hospitals are also available. In 2013, there were 422 physicians, 741 nurses and midwives, and 245 pharmacists per 100,000 population [10].

In the recent years, medicines and medical devices have been the fastest-growing component of public health care expenditure in Malta, the latter totaling 8.6% of the national gross domestic product in 2010. This is mostly due to ever-increasing medical care needs and the advent of new generations of drugs and products. The government supplies medicines listed in the hospital drug formulary free of charge to all in-patients in public hospitals. Other individuals entitled to free medication include pink and yellow card holders. Pink card holders (also referred to as Schedule II patients) benefit under the Medical Aids Grant of the Malta Social Security Act and entitlement is based on the total household income. Yellow card holders (also referred to as Schedule V patients) are individuals with a specific chronic condition listed in the Fifth Schedule of the Social Security Act. Dementia was included as one of the conditions in this list in 2012 with the subsequent introduction of the acetylcholinesterase inhibitor donepezil in the drug formulary.

Table 1. Life expectancy (LE), healthy life expectancy (HLE) and years lived with disability (YD) at birth based on mortality in Malta in 2005 and 2010 according to gender. Adapted from [11]

		LE	HLE	YD
Men	2005	77.2	68.6	8.6
	2010	79.2	70.2	9.0
Women	2005	81.4	70.4	11.0
	2010	83.6	71.6	12.0

Malta: an ageing population

Current projections indicate that Malta will be one of the fastest ageing countries in the European Union. The Economic Policy Commission's Ageing Report 2012 shows that the economic repercussions of this increase are also intensifying due to the interplay of longevity and shrinking of the labour force [12]. The effective economic age-

dependency ratio in Malta is projected to increase by 47% from 2010 to 2060, reaching 85%. The share of the population aged 65-plus in Malta is set to increase by 16.1% between 2010 and 2060, to reach 31.2%. The share of the population aged 80-plus population in relation to the population aged 15-64 will increase by 7.9%. This will result in an increase of the old-age dependency ratio from 24.1% in 2010 to 60.9% in 2060 [12].

The healthy life expectancy, based on mortality and morbidity combined data, shows an increase of 0.7 years for Maltese men aged 65 between 2005 and 2010. During the same period, an increase in healthy life expectancy of 0.9 years was observed for Maltese women at the age of 65, which in 2010 stood at 71.6 years and was the highest healthy life expectancy of women at birth in the EU. Healthy life expectancy of the Maltese men is ranked second highest. In 2011 healthy life expectancy at birth of women and men stood at 70.7 years and 70.3 years respectively, while its analogue at the age of 65 stood at 11 years for women and 11.8 years for men. This means that those men, who survive till the age of 65, have actually more healthy years of life than women at the age of 65. Considering men's overall shorter expectation of life, this makes a significant relative impact [11].

The United Nations probabilistic population projections, the 2010 revision based on the probabilistic projections of total fertility and life expectancy at birth, provide a range of values for the Maltese population between 2010 and 2060 [13]. From the data, it looks evident that there is much less uncertainty in the 65-plus projections where the absolute gap is less wide. This is due to the high life expectancy levels already achieved and no influence of fertility changes in these projected cohorts [11]. While the population aged 65-plus is projected to grow, the total population is declining rapidly from 2030 onwards. This results in an increase in the share of persons aged 65-plus in the total population, which reaches 37% in 2060. This is of particular significance in dementia where increased age is the most important non-modifiable risk factor.

Dementia in Malta

The first study to determine the prevalence rates of dementia in the Maltese Islands was published in 2007 [14]. Using the European Community Concerted Action on the Epidemiology and Prevention of Dementia (EURODEM) data methodology, it reported that in 2050, the number of individuals with dementia would reach 6,369, accounting to 2% of the Maltese population. This data was revised in another study published in 2012 [15] using the latest prevalence rates as reviewed by the EuroCoDe project (Table 2). The results showed that the estimated number of individuals with dementia in the Maltese Islands in 2010 was 5,198; a significant increase from the previous predicted data. Likewise, the number of dementia individuals over the age 60 in 2030 is projected to be close to 10,000 or 2.3% of the total population. Thus the 2% estimate will be reached in 2025, twenty-five years prior to what was previously reported. This discrepancy between the two prevalence set of data originates mostly from the oldest-old age groups, the latter being underreported in previous estimation studies. The significant increase reaching 3.6% of the Maltese population over the next fifty years will invariably put greater demands on the already stretched national health care services resulting in considerable socioeconomic consequences.

Table 2. Estimated number of gender-specific dementia cases in the Maltese Islands according to age groups using EuroCoDe data for the years ranging from 2010 to 2060. Data shown as M/F (M: males; F: females)

	Year						
Age groups	2010	2015	2020	2030	2040	2050	2060
60-64	30/139	27/124	27/127	21/100	27/123	29/127	25/105
65-69	179/154	240/201	223/186	217/177	198/164	234/193	246/185
70-74	242/346	246/344	381/513	376/493	292/391	382/488	419/507
75-79	367/577	419/601	446/616	671/871	677/847	639/800	777/959
80-84	448/834	493/945	620/1038	1100/1672	1154/1681	946/1380	1306/1784
>85	483/1399	619/1812	750/2248	1164/3021	2012/4806	2337/5400	2356/5368
Total IWD	5198	6071	7175	9881	12372	12957	14037
% of the population	1.24	1.47	1.73	2.37	3.04	3.26	3.62

State-run services for individuals with dementia and their caregivers are limited and currently not meeting the demands of the ever increasing number of diagnosed dementia cases. There are only two specially designed dementia wards, both manned by healthcare staff specifically trained in person-centred dementia care. Located within the premises of the largest long-term residential care facility in Malta is the dementia activity centre which was launched in 2007 and provides an opportunity of social interaction for residents and non-residents with dementia. Rehabilitation services, a Memory Clinic, respite care and a Dementia Helpline are also offered by staff comprising interdisciplinary healthcare professionals. With few exceptions, none of the privately owned residential

homes are dedicated to solely cater for the needs of individuals with dementia. In late 2012, in conjunction with the introduction of donepezil in the government formulary list, there was the setting up of dementia clinics in the community intended to offer support to the already existing Memory Clinic and the Cognitive Behavioural Disorders Clinic within the Neurology Department. Although free drug entitlement is only authorized by consultant geriatricians, neurologists and psychiatrists in patients with a Mini Mental State Examination score ranging from 13-26, all treatment options are available as an out-of-pocket expense from community pharmacies following prescription by any medical practitioner. To date, no protocol exists on the use of medication to control the behavioural and psychological symptoms of dementia (BPSD) experienced by the majority of these individuals. Interestingly, these drugs are rarely used in Malta among in-patients with dementia [16].

Dementia awareness and support in the community mostly comes from the Malta Dementia Society. This non-governmental, non-profit organization was launched in 2004 with the aim of increasing awareness on dementia care and management in the Maltese Islands through the organization of talks and seminars for individuals with dementia, their caregivers and healthcare professionals. Another important aim of the society is that of collaborating with the central health and social care authorities to improve and design new services that enhance the quality of life of individuals with dementia. As previously highlighted, most of the dementia care is provided by family members in the community. A study on the organization of dementia care in the Maltese Islands found significant difficulties in providing care for a relative with dementia [17]. Of particular interest is the fact that families have developed a rotating care pattern to accommodate individual family member's social and working life while still maintaining responsibility. Caregivers views of formal services were dismissive as to their lack of suitability for their or relatives' needs. This research continues to emphasize the need of expanding support services for people with dementia and their carers in the community.

Dementia policy development in Malta

Given the huge burden of dementia, the challenges facing governments worldwide are considerable. In these last few years, there has been an increase in recognizing the extent of this problem and the need to take action. Apart from Malta, only a few countries have dementia plans and policies in action that address the key medical, social and financial aspects that dementia pose on the society in general [7]. Priority areas for action common to these plans include increase in dementia awareness, access to social and health care, training of the workforce, support to informal caregivers, ethical and legal issues and enhancing research into prevention and treatment [7]. In the beginning of 2009, the Malta Department of Health through its Parliamentary Secretariat for the Elderly and Community Care launched the National Dementia Strategy Group with the aim of identifying a number of recommendations that would provide a strategic framework in order to deliver quality improvements in local dementia services and address any local shortfalls in dementia care [18]. This group was composed of an interdisciplinary team coming from the medical and allied health care professions together with representatives of the society. The work undertaken included (a) detailed analysis of services that are available to individuals with dementia and their caregivers, (b) consultation process with stakeholders working in the field of dementia management and care including professional bodies, and (c) questionnaire designed for the public in order to obtain information regarding the various aspects of informal dementia care. The findings together with the recommendations were presented to the health authorities in January of 2010.

Analysis of the dementia situation in Malta reported considerable lack of support at all levels of dementia care together with a dearth of healthcare staff professionally trained in dementia patient-centred care. Services available were not tailored for the needs of these individuals, their family members and caregivers especially if the person with dementia is still relatively young. Professional training at undergraduate and postgraduate level mostly focused on the medical model with very limited emphasis on social models of care. Basic awareness among the general population was found to be lacking with most individuals adopting a wait-and-see approach towards seeking professional advice [18].

The consultation process involved professional and nonprofessional stakeholders and included contact groups coming from the education sector (including academic bodies representing tertiary education), medical and allied healthcare representatives, acute and long-term health and social service providers and the community. The general public was invited to participate by sending feedback via a specifically drawn-up anonymous questionnaire that was available online and composed of twenty-five multiple choice questions analyzing the various aspects of dementia care within the community setup (Table 3). The topics focused on awareness and training, early intervention, government-supported structures and services, community support and end-of-life issues. A total of 613 completed questionnaires were analyzed as part of the report. Respondents were in the majority females and consisted of healthcare professionals, main carers, family members with no main caring role, individuals with dementia and other members of the public. The age of participants ranged between 30 and 70 years [18].

With respect to awareness and training, results demonstrated that dementia is not considered as a taboo subject among dementia caregivers, relatives and healthcare professionals even though the same categories pointed towards significant lack of public awareness. Issues hindering individuals suspecting dementia from seeking professional assistance included the belief that the symptoms will resolve with time, the presence of stigma that may lead to social discrimination and the assurance that such symptoms are part of the normal ageing process. Only a third of the respondents pointed out that healthcare professionals have the necessary training and skills in dementia care highlighting the need to enhance training in the various aspects of dementia management and care, possibly adopting a multidisciplinary approach that embraces both the medical and the social model.

In the majority of European countries, dementia is not diagnosed early in the diseases process and a significant time lag exists between observing the first symptoms and diagnosis. This is mostly due to lack of training among medical professionals necessary to identify the initial symptoms of dementia. During the stakeholders meetings, dementia caregivers expressed their concerns on the lack of advice and appropriate information at the point of diagnosis. Data from the public questionnaire exercise indicated a significant degree of reluctance to seek medical assistance following the appearance of the first dementia symptoms with a third waiting for more than six months before asking for advice. Stakeholders' intervention on issues relating to the availability of state-run services denoted a significant lack of basic infrastructure that provides adequate support to individuals with dementia. The number of purposely-built dementia units did not meet the demand and more community services were required to limit early admission to long-term nursing care. Furthermore, carers and healthcare professionals working with individuals with dementia pointed towards the need to be supported at all levels to prevent physical and psychological burnout.

The significant majority of individuals who participated in the questionnaire agreed on the importance of respite care provision. Even though the dementia activity centre was offering assistance in terms of providing respite to carers and a socially engaging environment to individuals with dementia, the service was relatively unpopular. Studies show that most individuals with dementia live within the community [17]. This is of great significance in a small country like Malta in which senior citizens continue to live within the family structure. Due to the progressive nature of the most common forms of dementia, affected individuals can still remain active, especially in the early stages of the disease. Recommendations by stakeholders included the provision of good-quality community services that would defer institutionalization, psychological support for informal carers in coping with stress of continuous care, dementia-designed home care services, financial assistance in purchasing assistive technology and an increase in the carer's pension as dementia costs are significantly higher compared to other medical conditions.

Table 3. Percentage response from different categories of respondents (all categories, n=613) to a sample of questions on various aspects of dementia (n/a: no answer). Adapted from [18]

		yes	no	don't know	n/a
Is there enough awareness on dementia?	carer/relative	24.7	69.0	5.8	0.6
	individual with dementia	17.7	64.7	17.7	0.0
	healthcare professional	19.1	77.9	2.2	0.9
	others	26.7	51.8	19.9	1.6
Is there enough information on services that are available for individuals with dementia?	carer/relative	23.0	64.4	11.5	1.2
	individual with dementia	23.5	47.1	23.5	5.9
	healthcare professional	17.3	71.4	9.5	1.7
	others	18.3	55.0	22.0	4.7
Do healthcare professionals have the necessary skills in dementia management?	carer/relative	44.8	25.9	25.3	4.0
	individual with dementia	47.1	17.7	29.4	5.9
	healthcare professional	30.3	49.8	12.1	7.8
	others	34.6	20.9	34.6	10.0
Do you consider community care as important?	all categories	88.4	1.0	3.1	7.5
Do you consider respite care as important?	all categories	85.6	0.3	5.4	8.6
Does dementia impact on family finances?	all categories	77.5	3.1	4.7	14.6

As expected, the majority of participants to the questionnaire considered community and respite care as important. Furthermore, caring for an individual with dementia has a significant impact on family finances. Other issues that were explored included palliative care, end-of-life issues and ethical approaches to dementia management and care. Unfortunately, there is a lack of these services all across Europe [19] even though such provision of care is routinely offered to terminally-ill cancer patients and that palliative management preserves the dignity of the individual and supports family members in coping with bereavement. Lack of knowledge in this particular area was felt in the feedback obtained from the public with a significant number of respondents indicating

lack of knowledge on such themes. Although dementia raises a number of ethical concerns for individuals with dementia and the society as a whole, such issues have not yet been addressed. The report presented to the health authorities in 2010 included recommendations aimed at: (a) Improving awareness of dementia in the community (b) Facilitating early diagnosis and intervention (c) Providing information at the point of diagnosis and beyond (d) Increasing knowledge of services that are already available (e) Enhancing the quality of care in acute and long-term settings (f) Strengthen community support services (g) Providing end-of-life support services (h) Adopting an ethical approach in dementia management and care.

Although the national dementia strategy has been launched only recently, positive initiatives in these last years comprised the availability of one anti-dementia medication for free by the government, collection of data on the number of dementia cases, increased awareness through the publication of a number of information booklets and training sessions on dementia care to healthcare professionals and support staff working with individuals with dementia in long-term residential/nursing homes. In 2013, the Maltese government appointed a National Focal Point on Dementia with the aim of advising the local authorities on measurements that need to be adopted in order to improve the quality of lives of individuals with dementia, their caregivers and family members. This included the drafting of a dementia strategy for the Maltese Islands.

In recent years, a number of research initiatives were conducted in order to explore the level of local professional workforce knowledge on dementia management and care. Education and training of healthcare professionals are major requisites not only in enhancing awareness, timely diagnosis and service delivery but also in reaching the critical mass necessary to effectively implement the recommendations laid down in the policy document. Most often, knowledge on dementia at undergraduate level is variable, fragmented and lacks focus on the social issues involved in the various stages of disease progression. The old medical model is too restricted to respond effectively to the multifaceted and diverse nature of the condition.

The knowledge and attitudes of nursing students towards dementia has recently been investigated [20]. Because of the upward shift in the number of individuals with dementia, a significant portion of nursing students will come into direct contact with these individuals during their clinical placement and succeeding graduation. Apart from textbook knowledge, nursing professionals need to internalize positive attitudes towards individuals with dementia in order to lessen the negative stereotypes associated with this particular condition. The overall findings show that nursing students in Malta had adequate knowledge of dementia (Table 4) even though they lack information on dementia risk factors and caregiving issues. A positive relationship was reported between perceived satisfaction of their experience during clinical placement and attitude. The students' age was found to be an important factor on the degree of dementia knowledge and attitude scores with older students obtaining the highest values. In conclusion, this study highlighted the need for a better theoretical and experiential preparation in dementia care for Maltese nursing students. This can be achieved by introducing more training that focuses on learning needs possibly through the use of predefined case scenarios and role playing.

Table 4. Mean Alzheimer's Disease Knowledge Scale (ADKS) and Dementia Attitude Scale (DAS) scores according to year of study among Maltese nursing students (n=280, 61.3% response rate)

Mean scores	First year	Second year	Third year	All participants
ADKS (Maximum score: 30)	18.35	19.88	20.18	19.36
DAS (7-point Likert scale)	101.18	105.98	102.30	103.51

Research on dementia in primary care is limited even though general practitioners (GPs) act as first point of contact for individuals suspecting memory problems and thus have an important role in ensuring timely diagnosis. Notwithstanding the considerable drive in promoting educational programmes aimed at primary care levels, dementia remains largely under diagnosed [21] even though there is a consensus among healthcare professionals that early diagnosis is beneficial to the patient and helps in delaying institutionalization. Lack of training in recognizing the initial signs of dementia is one of the underlying factors as well as the confounding symptomatic profile. GPs are also not comfortable with disclosing dementia citing concerns that include erroneous diagnosis and psychological distress. Similar trends were also observed in a study investigating practices in diagnosis, disclosure and pharmacotherapeutic management of dementia among Maltese GPs [22]. In the majority of cases, participating practitioners felt that they do not have enough training and skills in diagnosing dementia even though most of them correctly recognized that memory and behavioural difficulties are important symptomatic signs that accompany the condition. This may have led to a number of practitioners adopting a wait-and-see approach to diagnosis with a consequent delay in early management options. Therapeutic nihilism was observed in those GPs with fifteen years or more experience in general practice thus creating a niche whereby individuals with dementia are getting undiagnosed and unmanaged. In contrast with other countries, referral to dementia specialists was considered only by a very small number of Maltese GPs presumably leading to a lower catchment rate compared to geriatricians, neurologists and psychiatrists. Dementia disclosure is uncommon with local GPs and when it occurs, the patient is rarely consulted. Preferences of drug interventions shifted depending on the level of cognitive deficit and years of working experience in primary practice. The general use of medication to control the behavioural symptoms of

dementia was found to be low and varied depending on disease progression (Table 5). The overall picture obtained through this study was that GPs need more training on managing dementia in the community. Given its unique geographical characteristics with close-knit communities, GPs working in Malta are in direct and constant close contact with their patients and thus may act as role players in providing improved quality care to affected individuals and their carers [22]. A need is also felt in providing continuing educational programmes in order for these professionals to be in a better position to face the growing number and increased needs of individuals with dementia in primary care.

Table 5. General practitioners (GPs) (n=193, 54.2% response rate) responses on Alzheimer's disease (AD) pharmacotherapy (AChEIs: acetylcholinesterase inhibitors). Supplements included ginkgo-containing agents, nootropics and vitamin E

		Percentage of GPs
What drug treatment would you consider as first choice?	Mild AD	
	AChEIs	47.7
	Benzodiazepines	0.0
	All-class antidepressants	4.1
	All-class antipsychotics	0.5
	Memantine	3.1
	Supplements	36.3
	No response	8.3
	Moderate AD	
	AChEIs	64.2
	Benzodiazepines	0.0
	All-class antidepressants	3.1
	All-class antipsychotics	1.0
	Memantine	11.4
	Supplements	10.4
	No response	9.8
	Severe AD	
	AChEIs	40.4
	Benzodiazepines	3.6
	All-class antidepressants	2.6
	All class antipsychotics	3.6
	Memantine	31.1
	Supplements	4.1
	No response	14.5

Empowering change

In April of 2015, Malta officially launched its national dementia strategy entitled 'Empowering change: a national strategy for dementia in the Maltese Islands (2015-2023)'. It highlights various measures that need to be implemented in order to enhance the quality of life of individuals with dementia, their caregivers and family members. The multifaceted nature of dementia necessitates a multidisciplinary approach to dementia management and care. The vision of this strategy is for people in various sectors of society to come together and create a system whereby individuals with dementia have access to the support and care they require. Dementia also has a profound effect on relatives and caregivers and thus the policy document also aims to address their needs as part of the holistic approach to dementia care.

The strategy outlines a number of actions that are necessary in the different priority areas of dementia management and care (Table 6). These include an increase in awareness and understanding of dementia, the provision of timely diagnosis, the availability of a trained workforce, improving dementia management and care, promoting an ethical approach to dementia care as well as strengthening research in this field. It is also the result of a wide consultation exercise with the general public and stakeholders representing various sectors of dementia management and care. This ensures that the national strategy for dementia is a living document which encompasses a strong commitment from all those involved in order to empower change and make a true difference in the lives of people living with dementia.

Implementation of this policy document is scheduled to start in 2015 and run till 2023. Due to the challenging nature of dementia, this exercise will entail substantial investment in human, financial, technical and infrastructural resources. However, the gradual delivery of the objectives is projected to have a considerable positive impact on the quality of life of individuals with dementia, their family members and caregivers. The latter are carrying an enormous burden and thus require more solidarity from the government and society in general. Implementation of the measures set out aims to create a system whereby all individuals with dementia have access to the care and support they require.

Table 6. Streams of actions, objectives and main recommendations of the National Strategy for Dementia in the Maltese islands (2015-2023)

Actions	Objectives	Main recommendations
Increase awareness and understanding of dementia	Changing the perception of dementia Encourage help seeking Provide guidance	Continuing information campaigns Appointing Dementia Activists Online guide on dementia caregiving Promote the work of civil society organizations Strengthening of the Dementia Helpline
Timely diagnosis and intervention	Improve diagnosis at an early stage Provide information on available services upon diagnosis Timely access to care	Promote the value of early diagnosis in primary care Enhance training in dementia diagnosis, disclosure and management to primary care physicians Setting up of Dementia Intervention Teams Development and distribution of information at the point of diagnosis and beyond
Workforce development	Ensure health and social care professionals working with individuals with dementia receive specialized training	Provision of dementia patient-centred care training to the workforce Supporting information technology platforms that facilitate online training Continuous professional development programmes
Improving dementia management and care	Availability of all dementia medications on the drug formulary Improve care delivery Provide community support Implementation of dementia-friendly measures	Full access to medication and regular review Establishing training opportunities in non-pharmacological methods Ensure individuals with dementia have a care plan Involvement of all stakeholders in decision taking Increase respite facilities Implementation of dementia-friendly design Availability of palliative care support Ensuring the necessary quality standards in residential/nursing settings
Ethical approach to care	Promote an ethical approach to dementia management and care	Provision of training in ethical decision taking, respect for personhood and wellbeing Promoting the use of advanced directives Provision of psychological support services Adoption of the 'partners in care' approach Monitoring of abuse
Research	Promote and foster research in the field of dementia	Ensure that dementia becomes a national research priority Facilitate access to clinical trials Enhanced participation in European and pan-European research projects on dementia

The objectives laid down will also need the extension of a trained workforce in order to deliver new and improved services. It will also require joint planning and working between health and social care staff, policy makers, individuals with dementia, their families and caregivers. Continuous assessment of the outcomes, including real-life experiences of individuals with dementia, will ensure that the objectives set out in this document are met. Assessment should also seek the views of caregivers and healthcare staff. Since important gender differences exist across various aspects of dementia, with women mostly affected both in prevalence and caregiving [23], the implementation strategy will also strive to provide a gender dimension in its deliverables.

During the implementation process, a number of gaps may become apparent. Interim evaluations are thus necessary to gather new information and assess the usefulness of different projects being proposed in the various areas of dementia care. This will aid in further detailed planning of long-term objectives. Moreover, the implementation exercise is expected to reveal other important needs that will require assessment and further plans to adequately address them. A national team will be needed to coordinate and oversee the implementation process. Individuals with dementia, their family members, caregivers and policy makers all expect to see progress in a cost-effective way. It is therefore important that the results achieved are regularly communicated to the general public in an efficient and comprehensible manner.

Conclusion

There is little doubt that dementia will pose one of the greatest societal and health challenges that must be addressed nationally as well as at personal and family level. In general, there is a significant lack of awareness, training and support services in many aspects of dementia management and care in Malta. This is to be expected, considering that meaningful discussion on dementia at a national level kicked off only in these last few years. The

huge costs of the disease will challenge health systems worldwide with the predicted increase in the prevalence rates in line with an ageing population. Dementia is also overwhelming for family carers who often feel that they are left to fend on their own due to the lack of adequate support that promotes independence and wellbeing. Community support is needed to enable informal carers to continue in their caring role for as long as possible and should involve respite services and financial support. Moreover, training for healthcare professionals should be expanded and include multidisciplinary educational programmes focusing on patient-centred dementia management and care. The organization of effective campaigns that enhance public understanding of dementia will not only reduce misconceptions, stigma and discrimination but will invariably aid in timely diagnosis and help seeking. Political commitment is needed to generate and implement policies that work for these individuals and for those who care for them. The launch of a national dementia strategy aimed at holistically addressing important issues relating to increase in awareness, enhanced training for informal carers and healthcare professionals, and provision of the much required services at community level will undoubtedly have a positive impact on the quality of life of individuals with dementia in Malta.

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Psychological and physical benefits of traditional dance programs in elderly with dementia: theoretical approaches and research results

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Abstract

Dancing, as an aerobic exercise, contributes significantly to the overall physical and cognitive health of the elderly. Besides the physical benefits of dance such as the enhancement of strength, speed, flexibility, balance as well as avoidance of falls, it is also considered to have an important contribution to cognitive health. Dance intervention programs, implemented in patients with dementia, were found to improve their cognitive function and combat depressive symptoms. The combination of music, has a positive effect on cognitive functions such as intelligence, memory, concentration, etc. Dancing strengthens group activity, creates the need to externalize emotions and promotes sociability. We have implemented a program of traditional Greek dances in 41 elderly people aged over 60 (34 women and 7 men) with an average of age (69.43, SD = 8.02) and an average span of education (9.12, SD = 4.45). The diagnosis for most participants was Mild Cognitive Impairment (MCI), 4 patients with Alzheimer's dementia, 1 patient with schizophrenia as well as 9 healthy participants. The interventions lasted 24 weeks (48 sessions, 2 times / week, 60 ') and were held at both the Greek Association of Alzheimer Disease and Related Disorders and the Day Care Centers of Municipality of Thessaloniki. The traditional dances that were selected were from all over Greece, with moderate, progressively increasing intensity, indicative of the age and physical abilities of the participants. The effects of the intervention program on physical condition showed statistically significant differences in the strength of the legs and the dynamic balance (p = 0,000), the flexibility of low back and hamstrings (p = 0,000), the speed, agility and balance during movement (p = 0,000), the aerobic endurance (p = 0,006) and the reduction of body fat (p = 0,005). The results of the analysis for the cognitive functions showed improvement in the daily functional ability (p = 0,011), the selective attention (visual and acoustic - p = 0,034), the fluency (p = 0,000), the visual perception and the memory (p = 0,000). In conclusion, we would say that the Greek traditional dance is an important tool to combat health problems and generally it has a positive effect on the quality of life of the elderly.

Introduction

Dance is considered to be one of the most popular activity for elderly, as it is not just an enjoyable physical experience, but also a physical activity that cause functional changes in various systems of the human body, psychological benefits and can make the exercise more interesting and entertaining, by combining multitasking kinetic shapes, accompanied by music. There are many styles of dance such as modern, jazz, classical and traditional. Traditional dances have a wide variety that varies from different countries in the steps and music, performed under different social conditions and in different formats.

For the elderly people, dancing is a pleasure, concerning the exercise capacity, companionship, emotional balance, wellness, coordination, muscle tone and a romantic echo of their youthful years. Music is another important component of pleasure, as people enjoy it and expressed their selves through this. In addition, dancing with family members can strengthen family relationships, while dancing with friends can expand their social circle. The rhythmic music, improves coordination of walking and proprioceptive movement control in people with neuromuscular and skeletal disorders and leads to the enhancement of mobility and stability. Mild dance activity can prevent the risk of high blood pressure, diabetes, cardiovascular diseases. Improves bone density [1], improves flexibility of the joints, especially of the legs, as all muscle groups are exercised through a combination of steps, slow and fast [2]. Although it promotes euphoria, mild dance activates muscles, accelerates strength and perfusion of the heart, increases the combustion and thus affects the metabolism, increases the maximum oxygen intake, improves myocardial contractility, increases the frequency of breathing [1-3].

Dance is a form of body language. It carries the healing ability of symbolism, leading to dance therapy. The body, through dance, becomes the vehicle for someone to pass from Nature to Culture. Aiming, therefore, in a multidimensional body where all levels are presented: biological, social, psychological, artistic and religious. An activity physical and mental, individual and collective, representing sports and art, entertainment and spiritual practice [1]. Dancing is an excellent choice of physical activity. Requires simultaneous operation of both cerebral hemispheres, while also activates kinesthetic, logical, musical and emotional processes. For this reason, dance as a physical activity, reduce 76% the risk for dementia. The standard steps and specific figures do not help much. Creativity in dance is offering more results [4].

The correlation between physical and mental well-being, and the perception that physical exercise helps to maintain health [5], was made since the ancient years. The contribution of exercise is very close to the goals of the World Health Organization, for health which is defined as a state of complete physical, mental and social well being and not merely the absence of disease or infirmity [6].

Nowadays, is scientifically proven that participation in physical activity is an important factor that contributes to emotional balance promoting psychological situation of trainees [6-13] and is the best preventive agent for diseases such as arteriosclerosis, hypertension, cardiovascular disease, diabetes mellitus type II, osteoarthritis, osteoporosis, obesity, some forms of cancer, discomfort in the digestive system [14, 15].

Regular aerobic exercise, such as dancing and other physical activities such as walking, jogging and swimming, is beneficial for the overall physical and mental health of both adults [16] and the elderly [17]. Sedentary lifestyle (which is one of the risk factors for heart disease), promotes inactivity, atrophy and the organic sub functionality of older people significantly associated with the majority of elderly's deaths. Muscular atrophy of these individuals due to inactivity and immobility of the body can be reversed by the appropriate stimulus of physical activity, so that the person does not allow the body function to decrease to a level in which everyday life becomes difficult [18, 19].

In order to safeguard the health of elderly people, low intensity type of aerobic activity is recommended compared to the high intensity type leading to avoidance of potential orthopedic problems and cardiovascular complications [20]. Every type of continuous physical activity, in rhythmic and aerobic form, in which large muscle groups are involved, is considered to be cardiovascular exercise. For the elderly people, the exercise intensity of 30% -75% of VO2 max and over 30 to 60 min [21] is recommended. Aerobic exercise with lower intensity and longer duration produces comparable benefits to those achieved by exercise of higher intensity and shorter duration [22]. This form of exercise is dancing, which is considered to be the evolution of the natural movement of human. The dance is the physical movement performed rhythmically accompanied by music and at the same time is a life activity. Those who love dancing want to dance forever and in this sense significant adjustments during their lifetime are made. The dance is therefore a psychic experience with many physical benefits [23].

In a culture where technology is evolving at a very fast growth, the educational and spiritual level of the people is changing rapidly and people are living in a constantly changing environment, with the elderly people to become the biggest problem to conform. They have to learn new things and adjust to situations that until now were unknown to them. The exercise is directly related to the improvement of mental health of people of all ages, like the elderly people. Exercise and participation in physical activities act positively to reduce anxiety, depression and tension and contribute to personal satisfaction from life, optimistic attitude of life and against small or large daily problems of elderly people. It is very important for people in this advanced age to be able to live and move independently, without the assistance of others. The satisfaction they feel that their body still holds out, boosts self-esteem, self-confidence and enhances the confidence that they can still be creative and capable of many other everyday things, contributing thus to the quality of life [24].

The exercise of the elderly is not aiming exclusively to physical workout, but also to prevention and treatment of various diseases, release of emotions, creation and empowerment of relations. One way to achieve all these is the use of motion and especially of dance, which is a key therapeutic intervention tool for the elderly, and has various positive physical, psycho-emotional and social effects [25].

Quality of life is a complex concept, expressing subjective experiences, perceptions and needs rather than objective situations of life. It is directly linked to physical and mental health, sense of independence, good social relationships and opportunities for fun and finally to the ability of the body having the necessary strength, agility and vitality during normal daily activities in order not to be tired. Participation in physical activity and regular exercise contributes significantly to the quality of life by providing the people a personal meaning, and by helping them to elevate their mental wellness, increase positive mood, search for pleasant and intense experiences, improve their health and physical status and in parallel control their stress [24].

Concerning the elderly people, through dance they can externalize a great amount of their energy. When the elderly people start to deal with their bodies feel years younger. Both the dance and the improvement of their physical presentation would be a form of their good lifestyle, and through dance a possibility of limiting chronic diseases is provided [26]. So, in recent years most elderly began to participate in dance activities, not only to rekindle the passion of their youth [27], but mainly to promote their health, which is the main motive for the participation in exercise programs [28].

According to the literature review it was found that the dance not only promotes the improvement of the fitness level of the elderly, but also supports a lifestyle with active participation in activities and helps in general to limit both the occurrence and development of health problems. This is particularly important not only for the elderly who have experienced health problems, but also for healthy people. The dance is considered to be a mean of preventing health disorders.

In the survey of Federicil [29] a dance program in a group of elderly within three months was applied, in order to improve their balance and prevent or reduce falls. There was a second group without intervention, the control group. The tests used included: Sit up and Go, Tinetti, Romberg, improved Romberg. Program participants showed enough improvement of balance due to the activity of dance, while the control group did not show any change. By regularly practicing into dances, the balance of the elderly can be improved, reducing falls and fracture risk.

In another study of Zhang [30], a comparison of individuals was made, who did not participate in any activity with individuals who participate in social dance groups in which dancers found to have stability in posture and quickest reaction time on foot to those who were over 60 years. In the survey of Wallman [31], 12 healthy women attended jazz dance classes for seniors. Their age ranged from 54 to 88 years at the time the program was applied was 15 weeks with a frequency of once class a week of 90 minutes. Subjects were tested at the beginning, middle and the end of the program using the Sensory Organization Test (SOT). The results showed that the interference

significantly improved their static equilibrium under the SOT. Another study, by Choi [32], with an exercise program over 12 weeks, it was found that it could improve muscle strength flexors and extensors of the knee and ankle, flexibility, agility and balance.

There is an increasing recognition that psychological interventions for people with dementia and their carers have some value. Neuropsychological assessments and an exploration of the literature point to the potential benefits of non-verbal body-oriented interventions, psychotherapeutic work with people because of the deterioration of their cognitive abilities. In a study of Hamill [33], 18 people (11 people with moderate to severe dementia and carers 7) consented to participate. The total time of intervention was 10 weeks with a frequency of once a week and 45 minutes duration. Weekly tracking sheets of progress of participants completed and the participants surveyed by the group for their views. The results showed that the therapeutic intervention had a positive impact to the overall well-being and mood of participants, including better concentration and people communication. That research was supported by a pilot study with therapeutic circular dance as psychological intervention oriented in the body for people with dementia and their carers. That pilot study showed that the participants seemed to benefit emotionally, socially and cognitively as a result of a dance movement therapy group. Deterioration expected in dementia, but the need for emotional connection still exists. Finding ways to stimulate and maintain social skills, emotional expression and association and trust in people with dementia and their carers is vital to improve their quality of life, regardless the stage of the disease. Psychological treatments that use movement and dance in dementia needs further study and consideration and series of methodologies to assess their impact are required.

The emotional reaction to the social dances and to the walks for people with dementia, was studied to better understand the reason, popularity, and the importance of all these activities for the patients. The social dance events and walks videotaped and analyzed with the philosophy of Husserl as a basis for analysis. Six people with dementia participated in the study. The results are described under four interrelated issues: 1) The body in exercise 2) The understanding of caregivers, the encouragement, and management of patients during activity 3) The mutual affection and communication and 4) Environmental conditions. The results are then synthesized into an overall assessment of the emotional situation observed and reported in relation to the activities. The study was conducted in a nursing home in Stockholm. The dance events were held once a month on a large recreation room and attended by 50-100 people, people who live in nursing home and their caregivers, for over 45 minutes. A band was playing music and the participants were sitting and listening to music or dancing. The walks were designed to include small groups of patients with dementia, according to their physical and mental capacity, level of dementia, for a daily walk together with their carers for 20-45 minutes. The researchers filmed social dancing and walks in order to identify and classify emotional reactions of the participants. Based on facial expressions, some body movements, posture, the eye contact, touch and tone of voice. Between the two interventions there were similarities and differences. The involvement of the body was more substantial, had a physical place to dance but was not applied when a wheelchair was used in walks. In dance, unlike walks, it was easier for the caregiver to encourage the patient to have mutual affection because of its pleasant atmosphere created, something that was less easy to set up with walks. The most important result was the emotional reaction that occurred when people with dementia moved their bodies, participating and forgetting their physical injuries. If caregivers understand the relationship between these measures and the range of emotional reactions caused in people with dementia, may improve the quality of these reactions [34].

The traditional dance is associated with the life of the elderly, it is a social influence in them, and in addition its execution promotes sociability, elegance, creates a feeling of pleasure, and while in parallel is connected with health, physical activity and mobility.

Also, the traditional dance tutorials do not require high operating costs or special equipment, are a leisure activity for all ages and also for the elderly constitute an activity that connects them with their past. Greek dances is an activity with mixed form of charge offered alongside pleasure, recreation, education and evidence based functional and psychological benefits. The Greek dances are characterized by diversity and complexity, since combinations of lower limbs movements and combinations of lower and upper limbs are dominant and vary in intensity and moves from other dance genres.

The Greek traditional dances, in addition to providing entertainment, classified as an aerobic activity that creates a burden but as part of normal adjustments [35]. Also classified as an aerobic leisure activity offering a variety in intensity and in rhythm, creating a pleasant climate during the exercise.

Studies have reported that the folk dances as a physical activity prevent mental decline and improve the coordination and control of body movements [36]. The participation of older people in sports not only helps them maintain their fitness but gives them the opportunity to socialize with other people regardless of age. The interaction with others kicks the feeling of loneliness, leading to the boost of their psychological condition. Also improve their self-esteem as they realized that they can participate in new skills.

The research aims to investigate the effectiveness of a training program of Greek traditional dances and the effects of physical and mental health of older people. The research is aimed at elderly people who have Mild Cognitive Impairment (MCI) in order to be able to contribute to the prevention of cognitive decline.

Subjects - Material Methods

We have implemented a program of traditional Greek dances in 41 elderly people aged over 60 (34 women and 7 men) with an average age of 69.43±8.02 and an average span of education 9.12±4.45. The diagnosis for most

participants was Mild Cognitive Impairment (MCI), 4 patients with Alzheimer's dementia, 1 patient with schizophrenia as well as 9 healthy participants. The interventions lasted 24 weeks (48 sessions, 2 times / week, 60') and were held at the Greek Association of Alzheimer Disease and Related Disorders and the Day Care Centers of Municipality of Thessaloniki. The selected traditional dances were from all over Greece, with moderate, progressively increasing intensity, indicative of the age and physical abilities of the participants. Information and guidelines were given, as well as consent forms was obtained before participation in the study, while the rights of participants are protected throughout the duration of the project.

The method of data collection was through neuropsychological tests that were selected as appropriate to enable it to determine with the greatest possible clarity the mental status of patients before the intervention (initial assessment) and after the intervention of dance (final assessment). For this reason, 15 different tests were used, which examine all cognitive functions (memory, reason, judgment, abstract thinking, complex skills, attention, concentration, orientation, visuospatial perception). The tests that were selected are nominally the following: MMSE, CDR, FUCAS, FRSSD, IADL, TEA, TMT, ROCF, RAVLT, RBMT, VFT, NPI, GDS, QOL-AD, BAI. These tests have been selected on the psychometric properties (validity, reliability) and the existence of weight for the Greek population, and for the repeat test there were parallel forms for each test.

The participation of an older person in the dance program allows after medical examination certifying that they may participate in moderate physical activity and they had good functional ability. Were excluded elderlies with heart problems, hypertension, respiratory insufficiency. For the physical condition and functional ability, they evaluated before and after the intervention, by tests were related with aerobic endurance, strength of the lower limbs and the dynamic balance, strength of upper limbs, flexibility low back and hamstrings, speed, agility and balance during movement, jumping ability, balance on one leg, body mass index and body fat percentage. The tests that were selected are nominally the following: Chair stand, 8 Foot Up And Go, Back Scratch, Arm Curl, Chair Sit And Reach, 2 Min Step, Balance One leg, Jumping ability.

Results

For the statistical analysis, was selected significance level equal to or less than 0,05. We calculated the comparison of the performance of the average per test between the initial and final measurement by t-test.

In the following Table 1 below (Paired Samples Test) are marked with bold the tests which have statistical significant results, less than 0,05.

The FUCAS test, examines seven parameters (understanding the problem, working memory, planning, time allocation, sequence, accuracy and completion of the task) through six daily activities which are: taking medication, using the telephone, shopping, travel on roads , personal hygiene and dressing. The FUCAS test, estimates generally the daily functioning of patients with dementia and mild cognitive disorder. The results were statistically significant (p=0,011). So, dance shown to maintain the functionality of patients which would be worsen significantly if they didn't do this intervention.

The TEA (6tels) test, examines the visual selective attention of the patient, that is the ability to control the space properly and maintain his attention on a particular thing for some time. The orientation in space and the possibility of visual perception is in the parietal lobe of the brain, which seems to suffer gradually from Alzheimer disease into more advanced stages of the disease [37] and the LBD and PDD in the earliest stages [38]. However, the possibility of maintaining attention on a specific target is a skill which is lost relatively quickly in demented patients, especially in patients with LBD [39]. In this test was shown statistically significant difference (p=0,005). Therefore, dance shown that helped participants to increase attention and concentration as to stimulate more the piece of their visual perception.

The RAV1 test, examines the immediate memory and whether the patient is able to use learning strategies [40]. The test allows a comparison between skill learning and retention. The results were statistically significant (p=0,047) and showed that after the intervention of dance participants were able to improve their levels of memory. The fact that the intervention of dance introduced positive results in improving the memory seems to be important, because the most common form of dementia is Alzheimer Disease, which mainly decreasing the hippocampus of the brain resulting in presented difficulties in memory.

The Verbal test (verfls), examines the speed with which the mind can work, to whether slowly moves based on age and to whether the patient is able to maintain verbal fluency. The verbal fluency seems to decline as the dementia progresses, resulting in advanced stages of the disease, patients can't possibly naming any word. In this test the clinician prompts the concerned to indicate as many words he can that start with the letter "s", without being these words names of people or places into one minute. Also important results observed (p=0,001).

The Verbal test (verfmo), examines that and previous test (verfls) with the difference being that takes averages of words that emerged from the trials of the letters "s", "a" and "x". Also showed significant results (p=0,045). The dance introduced positive results on the verbal fluency of participants, helped them to operate and think faster.

The tests that evaluated the physical condition of the participants and their functional condition, were obtained the following results in Table 2:

For the statistical analysis of the tests was used the statistical package SPSS version 19.0. Statistically significant results were found in the following tests:

- The Chair Stand test, is a physical performance and evaluates the functional capacity of individuals through the strength of the lower limbs and the dynamic balance. The statistical analysis of test Chair stand test, shows that there is a significant statistical difference between the initial and final measurement (p = 0,000). The strength of the lower limbs is important for activities such as someone get up from a chair, or get out by bus or car. The strength in the legs affects directly the ease with which elderly perform daily activities.
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Pair		Paired Differences			Paired Differences 95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	df	Sig. (2-tailed)
1	Pre-MMSE - Post-MMSE	0,348	1,849	0,386	-0,452	1,147	0,902	22	0,377
2	Pre-FUCAS - Post-FUCAS	-2	3,367	0,718	-3,493	-0,507	-2,787	21	0,011
3	Pre-s1MAP - Post-s1MAP	-3,316	8,635	1,981	-7,478	0,846	-1,674	18	0,111
4	Pre-s4viac - Post-s4viac	1,556	6,732	1,587	-1,792	4,903	0,98	17	0,341
5	Pre-s4viti - Post-s4viti	-1,2144	3,4441	0,861	-3,0496	0,6209	-1,41	15	0,179
6	Pre-s6tels - Post-6tels	1,26682	1,91068	0,40736	0,41967	2,11397	3,11	21	0,005
7	Pre-FRSSD - Post-FRSDD	-0,636	2,838	0,856	-2,543	1,27	-0,744	10	0,474
8	Pre-NPI - Post-NPI	0,083	1,929	0,557	-1,142	1,309	0,15	11	0,884
9	Pre-rav1 - Post-rav1	-1,13	2,581	0,538	-2,247	-0,014	-2,1	22	0,047
10	Pre-rav2 - Post-rav2	0,87	3,209	0,669	-0,518	2,257	1,299	22	0,207
11	Pre-rav3 - Post-rav3	-0,391	2,017	0,421	-1,263	0,481	-0,931	22	0,362
12	Pre final rav - Post final rav	-2,609	9,389	1,958	-6,669	1,452	-1,332	22	0,196
13	Pre-verbal - Post-verbal	-1,5	3,661	0,781	-3,123	0,123	-1,922	21	0,068
14	Pre-verfls - Post-verfls	-1,818	2,239	0,477	-2,811	-0,825	-3,809	21	0,001
15	Pre-verfla - Post-verfla	-1,318	3,969	0,846	-3,078	0,441	-1,558	21	0,134
16	Pre-verfmo - Post-verfmo	-1,35545	2,98123	0,6356	-2,67726	-0,03365	-2,133	21	0,045
17	Pre-rbmt1 - Post-rbmt1	1,087	3,157	0,658	-0,278	2,452	1,651	22	0,113
18	Pre-rbmt2 - Post-rbmt2	0,978	3,679	0,767	-0,613	2,569	1,275	22	0,216
19	Pre-rey - Post-rey	-0,9087	6,5934	1,3748	-3,7599	1,9425	-0,661	22	0,516
20	Pre-reydel - Post-reydel	-0,3636	4,1495	0,8847	-2,2034	1,4762	-0,411	21	0,685
21	Pre-GDS - Post-GDS	1	2,415	0,67	-0,46	2,46	1,493	12	0,161
22	Pre-BDI - Post-BDI	3,4	13,343	4,22	-6,145	12,945	0,806	9	0,441
23	Pre-BAI - Post-BAI	24,5	21,92	15,5	-172,446	221,446	1,581	1	0,359
24	Pre-PSS - Post-PSS	0,609	11,276	2,351	-4,268	5,485	0,259	22	0,798

Table 1: Paired Samples Test for Psychological Tests s tatistical analysis, showed the following significant results:

- The Chair Sit And Reach test, evaluates the flexibility of low back and hamstrings, which is important for good body posture, for normal gait patterns and various mobility functions, such as getting in and out of a bath or car. The effects of the intervention program on this physical condition showed statistically significant differences (p = 0,000).
- The Foot Up And Go test, evaluates the speed, agility and balance during movement. It is important to tasks requiring quick shunting, such as getting a bus on time or until you get to watch something in the kitchen, or to go to bathroom or to answer the phone. This test is considered important (p = 0,000) for activities like walking around people since its aim is to measure the speed, agility, and also the balance. Having better balance, the elderly feel more confident to live an active life and in combination with the speed directly affected self confidence in everyday activities.

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Weight_Pre -Weight_Post	,537	2,215	,346	-,162	1,236	1,551	40	,129
Pair 2	Height_Pre -Height_Post	,024	,418	,065	-,107	,156	,374	40	,710
Pair 3	BMI_Pre - BMI_Post	,19634	,85486	,13351	-,07349	,46617	1,471	40	,149
Pair 4	Chair_Stand_Pre - Chair_Stand_Post	-2,610	2,558	,400	-3,417	-1,802	-6,53	40	,000
Pair 5	Chair_Sit_And_Reach_Pre - Chair_Sit_And_Reach_Post	-4,561	5,325	,832	-6,242	-2,880	-5,49	40	,000
Pair 6	Foot_Up_And_Go_Pre - Foot_Up_And_Go_Post	,95829	,89807	,14025	,67483	1,24176	6,833	40	,000
Pair 7	Back_Scratch_Pre - Back_Scratch_Post	-,683	5,841	,912	-2,527	1,161	-,749	40	,458
Pair 8	Arm_Curl_Pre- Arm_Curl_Post	-1,415	5,153	,805	-3,041	,212	-1,76	40	,086
Pair 9	Two_Min_Step_Pre - Two_Min_Step_Post	-8,415	18,431	2,878	-14,232	-2,597	-2,92	40	,006
Pair 10	Balance_One_Leg_Pre - Balance_One_Leg_Post	-5,16902	20,51607	3,20407	-11,64469	1,30665	-1,61	40	,115
Pair 11	Hand Grip_Pre - Hand Grip_Post	-1,289	4,876	,791	-2,892	,313	-1,63	37	,112
Pair 12	Jumping_Pre - Jumping_Post	-,711	2,804	,443	-1,608	,186	-1,60	39	,117
Pair 13	Body fat_Pre - Body fat_Post	-2,29526	4,75797	,77184	-3,85917	-,73136	-2,97	37	,005

Table 2: Paired Samples Test for Body Tests

- The 2 Minute Step test, evaluates the aerobic capacity and shows statistically significant results between the initial and final measurement (p = 0,006). The aim of this test is to estimate the strength of the elderly. The resistance is considered important for activities such as shopping, walking a certain distance, and also for travel. Having physical strength, therefore more energy will enable the elderly to enjoy more things and be able to do more with less fatigue. So, the independence is maintained.
- The development of skinfolds measurements came as a result of investigations for the simplest and least expensive methods of assessing body composition. Body regions and / or skin-fold thickness used in a regression equation for predicting body composition. To measure the percentage of fat was used the method that measures the width of the fold of skin at various points of the body, the skinfold caliper, and based on these measurements and the equation of Siri, established the proportion of body fat percentage. The results were statistically significant between the two measurements (p = 0,005).

Discussion

In conclusion, the dance as a form of exercise, except that offers the increase in physical strength, helps maintain proper body posture, tones the muscles and improves fitness. Combined with the music, helps in express their feelings in combating stress and improves mental health. By repeating steps, the movement of the hands and the combined operation, dance helps to improve the cognitive processes. It offers the opportunity to come into contact with other people regardless of age. By socializing are created, dance can discard the feeling of loneliness and enhance their psychological condition. Important considered to improve their self-esteem as they realize that they can participate in new skills.

The Greek traditional dances described as an aerobic activity, beyond from the fun they provide, causing a surcharge in the context of physiological adaptations. Improve the coordination and control of bodily movements and constitute an important tool fight against health problems providing positive effects on perceived quality of life of elderly.

Finally, such as showed the results of the above tests the dance is an intervention especially important to maintaining cognitive functions, and also in intensifying the some features, too. Additionally, test results showed that dance contributes even in the improvement of psychology of patients. Dancing other than a form of physical exercise, which seems to be particularly important for protection against dementia and also to slow the progression of the disease, is also a means of socializing participants. Socialization in turn contributes to maintaining of a positive psychology, which may be a protective shield for dementia, and to protect patients with Mild Cognitive Impairment (MCI) from possible depression, which aggravates the situation of a patient with cognitive problems. Nowadays, where non-pharmacological interventions for the treatment of dementia play a very important role on the world stage, our research confirms - the previously conducted studies - who report the importance of dance.

For this reason it is proposed to create Greek traditional dance programs in gyms, in Day Care Centres for the Elderly and in all elderly access, to enable them to improve their health through a physical recreation activity.

The dances an alternative way of form of aerobic exercise in addition to their recreational form causing a charge within the limits of their physiological adaptations. The Greek traditional dance can be an important tool to combat health problems and at the same time an ally of health and quality of life of older people.

The authors declare that they have no conflicts of interest.

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Dyslipidemia and dementia

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Abstract

Dementia is a leading cause of morbidity and mortality in high-income countries. The most common causes include vascular dementia and Alzheimer's disease. Dyslipidemia is a major modifiable risk factor for cerebrovascular disease and therefore is involved in the pathogenesis of vascular dementia. On the other hand, management of dyslipidemia with statins reduces the risk for stroke. However, it is unclear whether statins also reduce the risk for vascular dementia and there are reports of memory loss related to statin treatment. Regarding Alzheimer's disease, accumulating data suggest that dyslipidemia might also play a role in this disorder. In addition, most patients with dementia have a combination of both vascular dementia and Alzheimer's disease, highlighting the importance of aggressive management of dyslipidemia in order to reduce the risk of developing dementia and potentially delaying its worsening.

Introduction

Dementia is a major public health problem [Lancet 2005 2112]. It is estimated that approximately 24 million patients worldwide suffer from dementia and the prevalence of the disease is expected to double within the next 20 years [1]. In Western Europe, 5.4% of subjects older than 60 years have dementia [1]. Each year, approximately 4.6 million new cases of dementia are diagnosed worldwide [1].

The main causes of dementia are Alzheimer's disease and vascular dementia, which represent approximately 60-80% and 15-20% of cases, respectively [1]. More than 13 and 30% of subjects older than 65 and 80 years, respectively, suffer from Alzheimer's disease [2]. The median survival of these patients is 6 to 7 years and Alzheimer's disease currently represents the 6th leading cause of death in the United States [2]. The number of deaths due to Alzheimer's disease doubled between 2000 and 2006 [3] and is expected to increase further due to the aging of the population, given that each year, 1 and 6-8% of subjects older than 60-70 and 85 years, respectively, will develop Alzheimer's disease [2]. Regarding vascular dementia, approximately 1-4% of subjects older than 65 years suffer from this disease [2]. The median survival of these patients is shorter than in Alzheimer's disease, ranging between 3 and 4 years [2].

Dyslipidemia is an independent risk factor for stroke and hence for vascular dementia. However, in recent years, accumulating data suggest that dyslipidemia might also be implicated in the pathogenesis of Alzheimer's disease. Nevertheless, it remains unclear whether management of dyslipidemia with statins will reduce the risk for vascular dementia or Alzheimer's disease. In the present review, the role of dyslipidemia in the pathogenesis of Alzheimer's disease and vascular dementia is discussed.

Dyslipidemia and Alzheimer's disease

The pathogenesis of Alzheimer's disease is not entirely clear. The most widely accepted hypothesis for the development of this disease is the amyloid cascade hypothesis. It is supported that the increased accumulation of β-amyloid peptides in the cerebral extracellular space and the formation of amyloid plaques induces synaptic dysfunction and neuronal death [4]. Moreover, this increased deposition of β-amyloid peptides adversely affects the structure of tau protein, leading to the formation of neurofibrillary tangles in the intracellular space, which in turn disrupt neuronal structure and function [4].

a. Preclinical studies

Preclinical data suggest that cholesterol is involved in the increased cerebral deposition of β-amyloid peptides. In vitro studies reported that elevated cholesterol levels in cerebral neurons are transformed to cholesterol esters by acyl-coenzyme A-cholesterol-acyltransferase (ACAT) [5]. This accumulation of cholesterol esters stimulates the release of β-amyloid peptides [5]. In contrast, ACAT inhibition reduces amyloid plaque formation in in vitro studies and delays the progression of cognitive dysfunction in animal models [5]. Moreover, high-fat diet increases β-amyloid accumulation in the brain in animal models [6,7]. In vitro studies also suggested that unesterified cholesterol stimulates the activity of enzymes that degrade amyloid precursor protein to amyloid [5]. Moreover, cholesterol is located on neuronal membrane in rafts, where amyloid precursor protein is processed. Increased intracellular concentration of cholesterol esters perturbs the recycling of cholesterol in the neuronal membrane leading to increased β-amyloid production, β-amyloid accumulation in the extracellular space and reduced β-

amyloid uptake by the neurons [5]. In addition to these effects of cholesterol on β-amyloid, cholesterol also regulates the degradation of tau protein by calpain, which represents an early defect in tau protein metabolism [5]. On the other hand, in vitro studies showed that high-density lipoprotein cholesterol (HDL-C) reduces the accumulation of β-amyloid in fibrils and attenuates its toxicity [8,9]. The role of hypercholesterolemia in the pathogenesis of Alzheimer's disease is also supported by the association between apolipoprotein E gene polymorphisms and the risk for Alzheimer's disease. Apolipoprotein E is the main cholesterol carrier in the brain and the ε4 allele is less capable of transferring cholesterol than other alleles [10]. Moreover, patients with this allele have higher levels of total and low-density lipoprotein cholesterol (LDL-C) [10]. Interestingly, the presence of one ε4 allele increases the risk for Alzheimer's disease 4-fold whereas the presence of two ε4 alleles increases this risk 14-fold [10].

b. Epidemiological studies

In small studies where autopsy was performed, elevated serum total cholesterol levels were associated with increased risk for presence of β-amyloid deposition in the brain of patients 45-50 years-old. This association was observed even at relatively low total cholesterol levels. Indeed, patients with total cholesterol levels of 200 mg/dl had 3-times higher risk for cerebral β-amyloid deposition than patients with total cholesterol levels of 180 mg/dl. Interestingly, this association was not observed in patients older than 50 years [11]. It was also shown that patients with Alzheimer's disease have higher serum LDL-C levels and lower HDL-C levels than patients without dementia, and also have higher cholesterol levels in the brain [12,13]. Moreover, in these patients, serum LDL-C levels correlate with cerebral β-amyloid levels [12].

Observational studies also suggest that elevated serum total and LDL cholesterol levels are associated with increased risk for Alzheimer's disease. In an early study in 1,449 40-64 year-old subjects, serum total cholesterol levels > 253 mg/dl were independently related with a 2.1-fold higher incidence of Alzheimer's disease at the age of 65-80 years [14]. In a more recent and larger study (n = 9,844 middle-aged subjects), even at lower total cholesterol levels (> 220 mg/dl vs. < 200 mg/dl) there was an increased risk of developing Alzheimer's disease after 30-45 years of follow-up [15]. In addition, elevated serum LDL-C levels before the diagnosis of Alzheimer's disease are associated with more rapid cognitive decline after the onset of disease [16]. In contrast, HDL-C and triglyceride levels before disease onset do not predict the rate of cognitive decline [16]. In a meta-analysis of 5 prospective studies (n = 14,331) with a mean follow-up > 15 years, elevated serum total cholesterol levels at middle age were associated with a 1.4-3.1 times higher risk for Alzheimer's disease [17].

In contrast with these findings in middle-aged subjects, the relationship between cholesterol levels and the incidence of Alzheimer's disease in older populations is more controversial. In an early study, elevated serum total cholesterol levels in subjects 70-79 years-old were associated with reduced risk for developing Alzheimer's disease at the age of 80-88 years. However, this risk reduction was observed only at relatively high total cholesterol levels (> 264 mg/dl). Serum triglyceride levels had no predictive value [18]. In contrast, other studies did not confirm this association between total or HDL cholesterol levels in elderly subjects and the incidence of Alzheimer's disease [19,20]. In the above mentioned meta-analysis, elevated serum total cholesterol levels in subjects > 65 years were also not associated with increased risk for Alzheimer's disease [17].

The findings of these epidemiological studies are limited by the need for long-term follow-up and by the lack of consensus on the diagnostic criteria for Alzheimer's disease. Moreover, most studies measured only total cholesterol levels and could not disentangle the effects of different lipids on the incidence of the disease. It is also possible that some studies, particularly in the elderly, included subjects who already had milder forms of Alzheimer's disease at enrollment. It should also be emphasized that more than 40% of patients with Alzheimer's disease have clinically important cerebrovascular disease. In addition, almost all patients with vascular dementia have increased cerebral β-amyloid deposition, particularly those older than 80 years [4]. Accordingly, in most patients, dementia is caused by both Alzheimer's disease and by vascular disease [10]. Therefore, studies that evaluated the association between dyslipidemia and the risk of Alzheimer's disease could not differentiate whether patients developed only Alzheimer's disease or dementia due to both disorders.

Dyslipidemia and vascular dementia

Each year, almost 800,000 patients in the US suffer an ischemic stroke [21]. At 6 months after stroke, approximately 46% of patients older than 65 years have cognitive impairment [22]. In a meta-analysis of 61 epidemiological studies in the general population (n = 892,137), elevated total cholesterol levels are associated with increased risk for ischemic stroke in subjects 40-60 years-old, but this relationship is attenuated in older subjects [23]. In a more recent meta-analysis of 10 prospective studies in the general population (n = 238,739), each increase in serum HDL-C levels by 10 mg/dl was related with an 11-15% reduction in the risk of ischemic stroke [24]. In another meta-analysis of 17 prospective studies in the general population (n = 140,788), each rise in serum triglyceride levels by one standard deviation was independently associated with a 10% increase in the risk of ischemic stroke [25].

In addition to the association between dyslipidemia and ischemic stroke, epidemiological studies also showed a relationship between dyslipidemia and vascular dementia per se. In a cross-sectional study in the general population (n = 9,294), subjects with hypercholesterolemia had 43% higher risk for vascular dementia [26]. In contrast with the biphasic association between hypercholesterolemia and Alzheimer's disease, elevated total cholesterol levels are related with increased risk for vascular dementia in all age groups. Indeed, in a prospective

study in 9,844 subjects 40-45 years-old, subjects with total cholesterol levels between 200-239 mg/dl had a 50% higher risk for developing vascular dementia after 30-45 years of follow-up compared with subjects with total cholesterol levels < 200 mg/dl [15]. In another prospective study in older subjects (> 65 years-old, n = 4,316), elevated LDL-C levels and lower HDL-C levels were again associated with increased incidence of vascular dementia [27].

Statins and dementia

There are limited data from randomized controlled studies on the effects of statins on the prevention and management of dementia. In the Heart Protection Study (n = 20,536 patients 40-80 years-old with established cardiovascular disease or type 2 diabetes mellitus), the incidence of dementia or cognitive impairment during a follow-up of 5 years did not differ between patients treated with simvastatin 40 mg/day and those treated with placebo [28]. In the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER)(n = 5,804 patients 70-82 years-old with established cardiovascular disease or cardiovascular risk factors), the rate of cognitive decline after a follow-up of 42 months was similar in patients treated with pravastatin and in those treated with placebo [29]. In a recent meta-analysis of 4 randomized controlled studies in patients with Alzheimer's disease (n = 1,154), statins had no effect on cognition [30].

Conclusions

Experimental data and epidemiologic studies suggest that dyslipidemia is implicated in the pathogenesis of Alzheimer's disease. Moreover, dyslipidemia is a well-established independent risk factor for ischemic stroke and hence for vascular dementia. However, there are limited data regarding the effects of lipid-lowering treatment with statins on the prevention and management of dementia. Given the rising prevalence of these disorders, there is a clear need for more mechanistic, epidemiological and interventional studies on the topic that will elucidate the relationship between dyslipidemia, Alzheimer's disease and vascular dementia.

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The effect of mental empowerment and intergrative psychotherapy in patients with dementia

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Abstract

Aim: The main objective and purpose of this research is to investigate the influence of cognitive empowerment and psychotherapy in people with dementia, where a group of them have received assistance with the process of Psychotherapy and Mental Empowerment and the other team has not accepted any of such intervention. The general purpose of the present research is to examine possible relationships between the mental empowerment, the intergrative psychotherapy and the demented people. The Mental Empowerment influences in a greater extent the people with dementia and after the implementation of the Intervention. **Tools and Method**: The persons who participated in this research were N= 60 in total and all of them suffered from dementia. 30 persons were at an intervention plan in order to strengthen their mental status, while the rest 30 were out of intervention. The MMSE and the GDS were administered individually to all participants. It should be noted that the measurements listed in the practical part of the analysis have been carried out in three (3) phases: one at the beginning of the intervention, one after six (6) months and one at the end of the intervention, after a year. In order to process the raw data, the SPSS statistical package, version 17.0 was used. For the parametric analysis, the assumptions of normality and sphericity were tested using the Kolmogorov-Smirnov analysis. The analysis revealed that an intervention plan including mental empowerment will improve the cognitive abilities of demented patients at the specific stage of their illness. **Results**: Moreover, it was proven that an intervention plan including integral psychotherapy will improve the mood of demented patients at the specific stage of dementia. **Discussion** Overall, it was proven that the influence of Mental Empowerment and Integrative Psychotherapy in people with dementia is significant and capable of improving these people's quality of life.

Introduction

By definition, dementia, describes the symptoms that are observed in a large group of diseases. These symptoms are characteristic, because they create a gradual decline in human functionality. This term, however, is a general term, which is used to yield the loss of memory, intellectuality, reasoning sociability and other physiological, emotional reactions of individuals [1].

Most of the people that suffer from dementia are at an older age. It is important, though, that it's not necessary for the older people to have dementia, regardless of their age. It occurs, usually, in people over the age of 65. Nevertheless, it is possible that there are people aged 40-45 years and suffering from dementia. The forms of dementia are too many and different [2], such as F.T.P., A.D., P.D.In its many forms, dementia is a leading cause of functional limitation among older adults worldwide and will continue to ascend in global health importance as populations continue to age and effective cures remain elusive [3] estimated that over 2.5 million Americans suffered from Alzheimer's disease (AD) and that nearly 4 million had that and other forms of dementia in 2002. Given expected increases in the size of the older adult population, those numbers are expected to increase strikingly by 2050 (Alzheimer's Association, 2009).

Referring to the explanation of dementia syndromes and according to the basis of the studies carried out until today, it is argued that the main outcome related to dementia is that it is now considered as a "complex disorder, [3]. When referring to complex disorders, this means the contribution of one or more genes and environmental factors in the creation of the disease. The causes of the disease have not been determined adequately by the medical community [2].

Referring to the process of empowerment and Cognitive Psychotherapy in people with dementia, it could be noted that the international bibliography identifies some techniques which are related to skills and are applicable for careful observation, listening and influence during the interview process in demented patients [4]. From that time that these procedures are used by the therapist and can have positive effects in the interview in demented patients, are considered particularly important [5].

The rationale of the present study is based on the fact that mental empowerment and cognitive psychotherapy appear to be effective in many instances like brain damage, schizophrenia etc. Psychotic illnesses (for example, schizophrenia) and non-psychotic illnesses (for example, bipolar affective disorder and clinical depression) can place a substantial burden and stress on both the client and on the family as well as placing a considerable financial burden on the health care system [6], but, on the other hand, may be handled through mental empowerment and cognitive psychotherapy.

The main objective and purpose of this research is to investigate the influence of cognitive empowerment and Psychotherapy in people with dementia, where a group of them have received assistance with the process of Psychotherapy and Mental Empowerment and the other team has not accepted any of such intervention.

Additionally, it should be noted that the measurements listed in the practical part of the analysis have been carried out in three (3) phases: one at the beginning of the intervention or not, one in the middle after six (6) months and one at the end of the intervention, which means after a year.

Aims of the present study

The general purpose of the present study is to examine possible relationships between the mental empowerment, the intergrative psychotherapy and the demented people. The Mental Empowerment influences in a greater extent the people with dementia and after the implementation of the Intervention. The Psychotherapy affects the Mental Empowerment of patients with dementia after the implementation of the Intervention. Demented People need support from Intervention Programs aimed at the Mental Empowerment. This study might prove useful at a clinical level for demented patients. Intervention programmes in the future might include mental empowerment and cognitive – intergrative psychotherapy on a systematic basis. It was therefore, hypothesised that there will be significant differences in cognitive skills and mood between patients who receive an intervention programme including mental empowerment and cognitive intergrative psychotherapy, and those who do not.

Design

In the present research, a balanced and independent groups design was cosntructed. A fixed and non true independent variable, namely “Intervention”, included two levels, i.e. “With ME+ Cog” and “Without ME + Cog”, was studied. Two dependent variables were measured in interval scales a) Cognitive level and b) Depression. Therefore, this was a between subjects, paramentric, non – experimental, without premeasurement two way anova with repeated measures on one factor. A second factor “Time of Assesment” was also included, with three conditions, “Beginning”, “Middle period” and “End of Period” of intervention. This was a fixed and true indepentand variable.

Participants

For the purposes of this study, N=60 participants were recruited from the Nany Hospital, Neurological Clinic of Pireus. Therefore, an opportunity sample was used. n1=30 participants were receiving treatment with ME+ Cog and n2=30 participants were receiving treatment without ME+Cog. The research framework is fixed (Navy Hospital of Piraeus, Neurological Clinic), as well as the psychologists, the day and the time of the meetings. Participants are divided in two groups (consisting of 15 people each) depending on the MMSE. Their ages vary between 65 and 85 years old, and they are men and women. From the 30 participants, 20 are men and 10 are women. All participants are members of the Navy, with higher education level. The participants that accepted the intervention are 30. The same was the number of the people that did not accept intervention, mainly due to the distance. Moreover, the participants have steady life conditions, which means that no psycho – pressing event occurred to their lives (e.g. death of husband / wife or any other health related issue that could disturb their emotional status).

Tools

In this research MMSE was used along with the Geriatric Depression Scale (GDS).

Procedure

Participants were examined individually in a specially prepared room of the Navy Hospital of Pireus. First, each participant was briefed about the main aims of the study and their right to confidentiality, as well as, their right to leave to study at any point for whatever reason. Then he/she was provided with the ethics consent form to sign. After that, they were examined first by MMSE and next by G.D.S. The whole process was lasting approximately 45 minutes every time. Finally, each participant was debriefed and reminded of the fact that he/she would have no access to any individual scores, but only to the overall result of the present study. All data were collected in the period from September 2012 to September 2013.

Research Limitations

The general limitations are concerning the time spent by the respondents and the care they showed in completing the questionnaires, as well as a possible lack of full understanding of the questions due to the absence of the person who conducted the investigation. In addition there is a doubt about the limit in the number of responses selected and the effects of the respondent at any consecutive identical responses which may lead to selection of other choice, less desirable where the answer can alter the meaning of the responses about it.

Results

In order to process the raw data, the SPSS statistical package, version 17.0 was used. For the parametric analysis, the assumptions of normality and sphericity were tested. The histogramme and the Kolmogorov-Smirnov analysis, confirmed the normality assumption for all three MMSE measurements and all three GDS measurements. More specifically, regarding the MMSE measurements the analysis revealed Z =0,801, p=0,543 for Sept12MMSE, Z =0,775, p=0,586 for March MMSE, and Z =0,930, p=0,353 Sept13MMSE. The overall mean value of MMSE of the group of demented patients (regardless the existence of intervention or not) was 20.73 with std = 5.3.

On the other hand, regarding the GDS measurements the analysis revealed Z =1,096, p=0,181 for Sept12DGS, Z =1,212, p=0,106 for MarchGDS, and Z =1,359, p=0,050 for Sept13GDS. The overall mean value of GDE of the group of demented patients (regardless the existence of intervention or not) was 8.20 with std = 2.97.
The sphericity assumption (see Appendix) was confirmed only for the MMSE measurements with Mauchly's W (2)=0,938, p=0,163.

The two-way ANOVA with repeated measures on one factor for the MMSE revealed a significant improvementin the with-intervention patients' overall cognitive abilities (MWithIntervention= 22,500) compared to those who did not receive intervention (MWithoutntervention= 19,400), with F(1, 58)=4,767, p=0,033 as shown in Table 1 and Table 2 below:

Table 1: The means and standard deviations of MMSE of the group of demented patients with and without intervention

Intervention Status	Mean	Std. Error
With Intervention	22,500	1,004
Without Intervention	19,400	1,004

Table 2: The Analysis of Variance of MMSE of the group of demented patients with and without intervention

Source	df	F	Sig.
Intercept	1	870,892	,000
Intervention Status	1	4,767	,033
Error	58		

Therefore, the hypothesis that an intervention plan including mental empowerment will improve the cognitive abilities of demented patients at the specific stage of dementia was confirmed. Furthermore, a significant interaction effect between the time of measurement and the Intervention Status was found for the MMSE with F(2, 116)=89,626, p<0,001. As shown in the plot for MMSE (see Appendix) the highest MMSE score is noted in the third measurement of MMSE, that is, after a whole year of the implementation of mental empowerment, in the group of demented patients who received mental empowerment intervention. By contrast, the lowest MMSE score is noted in the third measurement of MMSE in the group of demented patients who did not receive mental empowerment intervention. The two-way ANOVA with repeated measures on one factor for the GDS revealed a significant improvement in the with-intervention patients' mood (MWithIntervention= 7,033) compared to those who did not receive intervention (MWithoutntervention= 9,344), with F(1, 58)=11,742, p=0,001 as shown in Table 3 and Table 4 below:

Table 3: The means and standard deviations of GDS of the group of demented patients with and without intervention

Intervention Status	Mean	Std. Error
With Intervention	7,033	1,004
Without Intervention	9,344	1,004

Table 4: The Analysis of Variance of GDS of the group of demented patients with and without intervention

Source	df	F	Sig.
Intercept	1	589,683	,000
Intervention Status	1	4,767	,001
Error	58		

Therefore, the hypothesis that an intervention plan including integral psychotherapy will improve the mood of demented patients at the specific stage of dementia was confirmed.

Finally, a significant interaction effect between the time of measurement and the Intervention Status was found for the GDS with F (2, 116)=68,855, p<0,001. As shown in the plot for DGS, the lowest DGS score is noted in the third measurement of DGS, that is, after a whole year of the implementation of integral psychotherapy, in the group of demented patients who received integral psychotherapy intervention. By contrast, the highest DGS score is noted in the third measurement of DGS in the group of demented patients who did not receive integral psychotherapy intervention.

Discussion

Dementia describes the symptoms that are observed in a large group of diseases. More specifically, the "dementia" tern is used to yield the loss of memory, intellectuality, reasoning sociability and other physiological, emotional reactions of individuals [1].

The main objective and purpose of this research was to investigate the influence of Mental Empowerment and Integrative Psychotherapy in people with dementia, where a group has received assistance with the method of Integrative Psychotherapy and Mental Empowerment, in contrast to another that hasn't received any such

intervention. In that framework, measurements have been carried out in three (3) phases: one at the beginning of the intervention or not, one in the middle- after six (6) months- and one at the end of the intervention , which means after a year.

The importance of the aforementioned study is significant, mainly due to the importance of the specific disease but also because of the potential results of these intervention methods. First, as far as the importance of dementia is concerned, the forms of it are too many and different [2], such as F.T.P., A.D., P.D. Based on that variability, one could reach the conclusion that dementia is a leading cause of functional limitation among older adults worldwide and will continue to ascend in global health importance as populations continue to age and effective cures remain elusive [3]. The prevailing terminology determines dementia as the disease that causes memory impairment resulting from the patient's medical history, clinical examination or some neuropsychological tests. In most cases the symptoms and duration last longer than six months. These disorders are capable of affecting the activities of patients, which are daily, but even their social relationships [7]. Having that in mind, it is evident why the importance of studying such a disease as well as the ways to reduce its effects is justified. Additional reasons may be introduced by the numbers of people affected by diseases strongly related to dementia. For instance, over 2.5 million Americans suffered from Alzheimer's disease (AD) and that nearly 4 million had that and other forms of dementia in 2002 [3]. Given expected increases in the size of the older adult population, those numbers are expected to increase strikingly by 2050 (Alzheimer's Association, 2009), and thus the importance of studying means of reducing its effects increases.

One of the proposed means of reducing these effects, include Integrative Psychotherapy. Referring to the concept of Integrative Psychotherapy, we would say that this particular case comes under the psychotherapy process and subsequent relevant theoretical models [4]. According to the rules of Psychotherapy in demented patients is known that every psychotherapist necessarily creates a unique and personal shape which is psychotherapeutic. This fact is inevitable and forced to be created [5], and is critical regarding the investigation of the way that Integrative Psychotherapy can affect dementia.

In addition to the above, the aim of the Integrative Approach is for the therapist to familiarize and to be trained in many possible therapeutic schools [8]. In that framework, the therapist will be able to create his own theories and techniques that will always be composed with the words and the contexts of each patient. He uses the appropriate techniques and theories from some psychotherapeutic approaches, and then compose them into a shape that fits the needs and requirements of the patient. This provides the appropriate psychotherapy to be used as a means for dealing with the symptoms of dementia.

Based on all the above, the analysis carried out aimed at investigating the level at which the intervention that was carried out, affected the outcomes of both MMSE and GDS research tools. Participants were examined individually in a specially prepared room of the Navy Hospital of Pireus, and they were examined first by MMSE and next by G.D.S.

It was proven that a significant improvement in the with-intervention patients' overall cognitive abilities is feasible, compared to those who did not receive intervention. Having that in mind, it was proven that the hypothesis that an intervention plan including mental empowerment will improve the cognitive abilities of demented patients at the specific stage of dementia was confirmed. Therefore, it was proven that the symptoms of such a critical disease may be minimized through the process of intervention, which is based on psychotherapy and mental empowerment. In addition to the above, the analysis revealed a significant interaction effect between the time of measurement and the Intervention Status for the MMSE. More specifically, according to the outcomes of the statistical analysis the highest MMSE score was noted in the third measurement of MMSE, that is, after a whole year of the implementation of mental empowerment, in the group of demented patients who received mental empowerment intervention. By contrast, the lowest MMSE score is noted in the third measurement of MMSE in the group of demented patients who did not receive mental empowerment intervention.

This result actually strengthens the assumption that the intervention based on mental empowerment highly affects the outcomes of the MMSE, as these outcomes vary though a year. The results for patients receiving psychotherapy depict an increasing MMSE through the year, while the result is the opposite for patients not participating in the intervention program.

Another aspect that was investigated through the data collected from the patients was the one of the level of depression, by using the GPS research tool. More specifically, as in the case of MMSE, the results regarding the GPS research tool were compared with respect to whether the patient participated in the intervention program based on mental empowerment or not. As stated in the previous chapter, the analysis carried out verified the existence of a significant improvement in the with-intervention patients' mood with respect to the mood of those who did not receive intervention. In that framework, it was verified that the hypothesis that an intervention plan including integral psychotherapy will improve the mood of demented patients at the specific stage of dementia was confirmed. Thus, apart from the increase in the outcome of MMSE, such an intervention plan is likely to reduce the levels of depression in patients with dementia and as a result increase the quality of their life. Mental empowerment therefore as a means of dealing with demented patients is proven to be really powerful and efficient.

The last outcome of the analysis carried out within this dissertation was about the level of interaction between the time of measurement and the Intervention Status that was found for the GDS research tool.According to the outcomes of this analysis, the lowest DGS score is noted in the third measurement of DGS, that is, after a whole year of the implementation of integral psychotherapy, in the group of demented patients who received integral psychotherapy intervention. By contrast, the highest DGS score is noted in the third measurement of DGS

in the group of demented patients who did not receive integral psychotherapy intervention.

As in the case of MMSE, this result actually strengthens the assumption that the intervention based on mental empowerment highly affects the outcomes of the GDS research tool, as these outcomes vary though a year. The results for patients receiving psychotherapy depict a decreasing depression score through the year, while the result is the opposite for patients not participating in the intervention program.

Overall, it was proven that the influence of Mental Empowerment and Integrative Psychotherapy in people with dementia is significant and capable of improving these people's quality of life. Based on the outcomes of this research, it is obvious that such intervention methods (mental empowerment and integrative psychotherapy) should definitely be used in patients with dementia. The large variety of diseases related to dementia indicates that there are numerous patients that could exploit such intervention procedures in order to make their lives easier and minimize the effects of their illness in their everyday lives.

The authors declare that they have no conflicts of interest.

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The importance of treating dementia through art

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Keywords: Life quality -Dementia -Primary health care

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Abstract

Through the development of psychotherapeutic approaches and the establishment of cognitive empowerment programs we have managed to introduce treatment through art to the Dementia Intervention Program at the Naval Hospital of Piraeus - Memory Centre. **Aim.** The goal of this art intervention is both the prevention and the improvement of the psycho - emotional, hence the cognitive and the behavioral status of the patients. **Materials & Methods** The patients at the Naval Hospital of Piraeus - Memory Center are divided in groups according to their cognitive status based on the psychometric tools of MMSE, Verbal Fluency and Clock Test, and according to their psycho-emotional status based on the GDS, CSDD and HAM-A, HAM-D. Thus formed groups with Mild Cognitive Impairment (MCI) patients with (MMSE 26-30) and Mild Dementia patients (MMSE 20-25). The emotional state of all patients mainly anxiety and the depression was about the same extent (HAM-A: 18-20, HAM-D: 10-11) in all groups. Excluded patients with severe psychiatric symptoms. **Results** During the operation of the Memory Centre and based on the results of the assessment concerning the condition of the patients, statistically significant differences have been noticed, mainly in improving the emotional and behavioral status. The scales that assess their cognitive status seemed to stabilize or to improve while the mood of patients improved after each session significantly reducing stress and depression over time.

Introduction

Dementia disease primarily of older and widespread in our time, is a set of symptoms, associated with the cognitive functions of the brain and affect mood and behavior of the individual, which affect the daily life and quality of life but and people who live with him. The disease gradually progresses slowly or quickly for the worse. The symptoms are multiple and appear depending on the development stage of the patient in memory, thinking, language, mood and functionality. About the symptoms of memory, thought and language, the patient suffers from disorientation of time and space. Many times he has also confusing thoughts that makes difficult the communication with other people.

One of the most characteristic symptoms of mild dementia is the difficulty of spontaneous speech. Patient cannot recall the right words nor name objects. He often does not remember where his personal things are. Sometimes he confuse people names or he does not remember who is who. He often forget when got his medication or his medical appointments. By the same way a patient has many difficulties in daily functionality. The appetite and sleep disorder affect his physical strength and his mood. In severity dementia we meet patients who have difficulty on dressing. They can not snap buttons, wear the blouse correctly and combine clothes. Reduced functionality affects them anyway and hygiene as the patient may find it difficult to be consistent to some rules like to wash or use the toilet in time. Other symptoms that with the passage of time are that they can not cook, stay at home, get away from home alone, throw trash in the trash bin, to manage its finances, go shopping alone, pay accounts. They find it difficult to write, read, watch TV, participate in a discussion, sometimes talking about things that are unrelated to the topic or repeated so often with thoughts that are not coherent and do not make sense.

The realization of all these problems on the part of the patient affect the mood of creating mainly the most common symptoms of dementia such as depression and anxiety. The patients often start weeping or crying with tears very easily, feel dud, believe that the state of health is a punishment they deserve, are disheartened about the future and feel a burden on the family, often wishe to die. At the same time they appear possessed with extreme anxiety for no apparent reason. The patients are afraid and anxious about trifles, for scheduled appointments, seem to avoid meetings with relatives and friends, feel trepidation when separated from the "caregiver", have physical symptoms such as stirring in the stomach, palpitations etc. The patients often try to behave normal and hide the cognitive symptoms of dementia that even he understands they create great irritability. Easily disrupted, the mood is extremely changeable, have sudden outbursts of anger, become quarrelsome and difficult to socialize them. Sometimes they may even expresse frustration and even when they try to take care of.

All these of course are symptoms that may have been present with dementia or may arise because of it. The existence of even these symptoms in mood and behavior of our individual suspects to launch some form of dementia. However there are some signs that the root lies in the existence of the disease. So we meet patients with aberrant motor behavior. A behavior that its main feature is the repetition of movements such as n 'snap one wardrobes, drawers and doors in the house, looking then something inside the bag, pacing without apparent reason in the house, fasten buttons unbutton his clothes , to dress and undress.

At other times we have patients with a picture of excessive euphoria without reason, whereby man can be happy, to laugh with things that are not funny to make fun up comments offensive to third parties, using childish phrases and laughing inappropriately.

On the other side of this symptom is apathy where the person seems to have lost interest in the world around him, and is in a state of indifference. There are energetic in any normal activities, not easily participate in various business or social obligations. Difficulties also exist where disinhibition creates an impulsive behavior with things not said or done publicly (comments sexually or exposure to family issues), with consequences for the people of the nearby environment of the patient.

Nevertheless, the greatest difficulty for the patient and its surroundings create psychiatric symptoms such as delusions or hallucinations. According to what the patient thinks that the others, even family members, wanting to harm him, steal him, tease him. Is deeply convinced that danger, that his / her spouse might be cheating, that family members are not what they say they are, that even prepared to give up all of that persons TV or magazines of speaking and dealing with it . We may hear voices, see things that are not like animals, lights, etc., talking to people who are not present, to smell scents that do not exist to describe flavors that are unjustified, feel on the skin of walking or crawl things. So as we study the "world of dementia," and seeing the complexity of symptoms, we are trying to find new ways of intervention in treatment that are more related to the expression of emotions than with the use of speech and which take place mainly in the prevention of disease. Treatments through art include non-verbal interventions that can be used independently or combined to medication and psychotherapy as an alternative additional intervention. The common goal is to test an alternative way of expression.

Art contributes to the discovery, development and expression of those aspects that involve creative power. In terms of dementia the benefit is primarily creating positive emotions, desiring communication with other people and the environment, enhancing self-confidence, improving self-image, enhancing memory and, of course, improving the quality of life. The main types of treatment through art used at the Piraeus Naval Hospital Memory Center is music therapy, dance therapy, drama and visual art treatments that promote a person's cognitive, emotional, physical and social development enriching the emotions and the improvement of the behavioral condition of the patient, using speech as less as possible, and this is the reason it can be applied to patients with limited verbal ability.

Materials & Methods

Music Therapy

In music therapy we use music as a means of the therapeutic process connecting it to the human nature, since music is nothing more than rhythm and sound, intimate information that we meet at the first years of our life through our body. Rhythm is very familiar to humans from our breathing and heart beat or our own moves while sounds are produced while laughing, crying or speaking. [1]The goal is be in constant contact with the body, acknowledge and then recreate the feelings. What is very important is that it is not necessary to have musical knowledge. [3] Through music therapy we notice the revelation of personality elements that are expressed through several dynamic sounds and tone colors, and that's why we concentrate on the expression and feeling qualities of improvised music.[14] At the Naval Hospital of Piraeus, the Memory Day Centre, a typical exercise of music therapy intervention is the reproduction of sounds "motivated" by the patient's emotions.

The first phase of this exercise is to contact with the body. The patient is asked to listen to his body's behavior (the rhythm of his breathing or heartbeat, the tension he may feel etc.), and in the second phase to reproduce a sound with a musical instrument, usually a drum, a doumbek or a tambourine and sometimes the patient is asked to reproduce a sound with his voice, singing a melody or a song. The results of those two first phases of this exercise indicate the emotional status of the patient, since the sound that we hear helps us understand whether it contains fear, stress, anger, happiness or tranquility without the need to express any of these with words. Actually the therapist, by decoding musical characteristics like intensity and rhythm, tries to emotionally coordinate with the patient making him understand that any feeling is acceptable.

In reality, the therapist becomes a receiver of all these emotions trying to build a therapeutic relationship, gaining the trust of the patient and helping him gradually open and express himself firstly through music and then, if he wants and can, through speech. Thus, we enhance communication, speech and social skills. The lyrics of the songs are most of the times the phrases that we seek to find inside us to express our emotions and communicate and give a message to our social circle. In cases that the patient's feelings are negative we move to the third and last phase of intervention, which includes the listening of a song aiming to the relaxation in combination with breathing exercise.

Another exercise included in music therapy aiming to strengthen the memory, is learning songs and then remembering lyrics and memories.

Dance Therapy

In a similar way we work with dance therapy exercises, which are based on the suggestion that the body is tightly connected to the mind and soul. [5]As a result of the single three-dimensional human existence (body-soul-mind) it's considered that any change made to one of these three, will affect the others.

The basic tool in dance therapy is the body, and movement is the means of change. According to the principles of dance therapy, the body reflects personal history, personality and emotional state of one person and the movements express memories, experiences and how we react to them.[7] The main therapeutic factors are the body, the movement, the therapeutic relationship and elements related to music such as melody, harmony, pulse, rhythm and intensity. [6]

One of the dancing styles we use is traditional, which is directly connected to the culture of the patients, aiming to enhance healing through memories and doing memory exercises since patients are asked to remember the lyrics of traditional songs, melodies and steps from specific dances. Music evokes feelings and motivates the body to express, awakening whatever may be kept inside us by the refusal and the repulsion.

However in the Memory Day Centre program we included modern dance exercises through which we seek the spontaneous, authentic, and subjective expression of the body, shedding light on feelings that come to the surface. The results of this therapeutic approach are mainly the release of physical tension and anxiety, emotional development, the creation of a deep relationship and understanding of the body, the development of self-esteem and initiative, the enhancement of communication, the promotion of sociability and generally the improvement of the quality of life. Moreover, frequent neuropsychological tests allow us to speak of a statistically significant difference in the improvement of memory and executive functions of patients.

Drama Therapy

A program of therapy through arts couldn't exclude drama therapy, in which, by using the theater techniques, we improve the mental health of the patient aiming at clearance and revealing experiences, expectations, needs, aspirations. Examples include frequent drama therapy exercises in which the team coordinator describes a story and then gives roles to the patients in order to reproduce the story told. Each patient can express himself through the role, but he has to develop dialogues with the other members based on the main subject.

The completion of the story is followed by a discussion through which the members share emotions from this experience. What we notice is that through drama the participants can express their creativity, find solutions to personal problems, respond to questions that concern them, deal with their loneliness and manage negative emotion such as grief, stress concerning potential changes in their lives, fear of death.

Visual Art

Finally, with visual arts the patients participate in a healing process through the use of artistic media such as painting, clay, collage aiming to create a visual project. In the Day Centre we use the decoupage technique with which we create Christmas balls for the tree or frames in Christmas, candles and cards in Easter, and the rest of the year we create small boxes, vases and other little things. This enhances team members' self-esteem, their kinetic activity and increases positive emotions since the result proves that they can manage things as opposed to their original belief according to which they express weakness managing this exercise. Moreover, activities like painting and collage enhance free expression. The therapist gives the material needed and chooses the subject giving a word like "love", "summer" etc.

Team members spontaneously imprint their feelings coloring a white paper or collaging various pictures from newspapers and magazines based on the subject that the coordinator gave them. Each member's creation can be shared and discussed since it's directly connected to their feelings. Through visual art we aim to the emotional expression and well-being, the improvement of kinetic activity and implementing function, developing at the same time imagination and self-esteem.

Results

The results of these exercises are measurable with the use of short cognitive evaluation scales concerning the emotional status, that are filled by the patients before and after the exercises. They include questions such as "I rate my stress1 from 0 to 5" (0 means no stress and 5 full stress). Patients complete these scales before and after of art therapy 's exercise, At the same time use GDS scale that gives us an insight of the levels of depression and stress patients. Results indicate that patients with GDS 5-8 (mild depression) are now at 0-4 (normal),

At the same time every three months a neuropsychological check takes place in order to record statistically significant differences in terms of both cognitive and psycho-emotional status by measuring depression and stress. The tools we use are MMSE scale, Verbal Fluency and Clock Test which give us an insight into the cognitive level of the patient and HAM-A and HAM-D through which monitor the levels of depression and anxiety of patients in combination the CSDD (Cornel Scale), scale for depression in dementia.

Results the two last years show that the MMSE all patients with mild cognitive impairment and moderate stage of dementia, has stabilized and in some cases noticed a slight improvement (1-2 score on average). At the same time improving the Verbal Fluency Scale proves significant improvement in the skill recall of words. The CSDD is totaly less than 5. HAM-A reached from 19-20 reached to 12-14 and the HAM-D reached 11 to 8, that shows the emotional uplift and anxiety and depression reduction.

Discussion

Therapy through arts aims to the growth of self-esteem and initiative, creative expression, emotional support, communication enhancement, speech development, memory strength, sociability promotion, reinforcing specific skills that each person needs in order to develop its communication skills and build personal bonds, creating a therapeutic environment within which the person can experience and express various emotions, growing at the

same time the consciousness and understanding of his feelings, the improvement of quality of life through the experiences gained from the therapy and through learning to share, express, give and take, concentrate, focus and remember.

The authors declare that they have no conflicts of interest.

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The role of the educational games in enhancing cognitive function

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Keywords: Life quality -Dementia -Primary health care

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Abstract

Aim: The aim of this study is to investigate the correlation of educational games with the preservation or variation of indicators, studying people with cognitive disorders.**Measures:** The tools used for the conduct of the study is the scale Mini Mental State Examination (MMSE), the Verbal Fluency test, the Recall from Table 10 words test, the Geriatric Depression Scale (GDS). **Method:** This study lasted six months and involved a total of 20 people, aged 56-70. Distinction was made according to the mark of cognitive decline. Thus formed two groups of 10 people, A with the mild cognitive impairment and B with mild dementia. For the duration of 6 months, all individuals involved watched once weekly sessions of one hour. The first half hour solve Sudoku and the rest half an hour playing a construction game. Were tests in all patients at the start of the intervention and reassessment performed after 6 months.**Results:** After measuring the results observed changes in scale MMSE, the Verbal Fluency test and Recall from Table 10 words finally been changes in Geriatric Depression Scale. The results of this study show an improvement in immediate recall and concentration as demonstrated by the change in indicators. Additionally there is a change in the depressed mood of the participants. **Discussion:** The implementation of empowerment group enhancing cognitive functions through educational games in the context of non-pharmaceutical intervention, conducted at the Naval Hospital of Piraeus, confirmed the objectives of the intervention in a period of 6 months.

Introduction

Educational game is called a structured activity conducted for the purpose of entertainment or practiced as an educational tool. The games come in different forms such as table, computer games, intangible, materials etc. The essence of the game is the combination of its rules, the players' goals, as well as the challenge and interaction levels.The goal of the game in general is to stimulate the player mentally or physically, and often both. There is a number of games that help develop practical skills. They can take the form of exercise or have training, simulated or psychological nature.

The use of educational games aspires to provide mental training. This includes techniques such as problem solving, discussion exercises and speech production, periodical recall method, person connecting education - name therapy memories [1-3]. Through playing, social interaction, as well as expression and communication skills are enhanced, which helps the person to better form an image of himself, others and the world. Its role is essential to brain training and learning because it offers stimuli for observation, experimentation, investigation, forecasting, planning, interpretation, hypothetical, question generation, understanding, performance goals, and solving problems. Furthermore, when dealing with the game, a better perception of the body, its limits and possibilities is acquired, leading to developed body orientation and adaptation skills to the needs of the movement. All these effects of the spiritual game function as a unifying mechanism of holistic learning and development, as this activity integrates cognitive, emotional and social stimuli. It provides the meaning for the recruitment of new connections and relationships between ideas, experiences, skills and knowledge.

Noteworthy is the fact that the game has an essential role in the development of linguistic, cognitive, social and emotional skills, and reinforces the growing understanding of complex concepts such as size, shape, weight, rigidity and flexibility. Learning games are largely related to the development of fine and general motor skills. In addition, inventiveness, imagination, creativity and ability of solving all kinds of problems are encouraged. The mental game is important for the healthy mental and physical development [3-7]. Educational games encourage the development of logic and acquiring skills and knowledge in a pleasant way. Their background is associated with the part of knowledge that individuals have to apply in order to achieve the objectives proposed to them. The games are a source of motivation for people in order to test their knowledge, to develop it through its application and to learn things they did not know.

Enhancing cognition is achieved through these techniques arising from dealing with educational game. People are getting familiar with the basic concepts of space. They practice basic cognitive skills such as attention, observation, memory, perception, reasoning, and thinking. Specifically, the logical - mathematical thinking is exercised through their motivation to solve the problem and their desire to find a solution. Moreover, through most of the educational games reflection situations are created, and experimentation is used for appropriate solutions.
While taking part in these activities, it is noticed that attention and observation are developed, while mental abilities, combining ability and distinction of the importance of stimuli are largely practiced. Finally, the spirit of creation is cultivated and encouraged.

Cognitive training by using educational games is preventively proposed in people with mild cognitive impairment and in subjects with family history in cognitive disorders. Apart from strengthening the aforementioned functions, learning and strengthening of specific skills such as language development, listening and observation skills is also enhanced. The person's ability of receiving and giving complex instructions, his memory skills and reflection capacity, his ability of creating new rules and lifestyles, cooperation skills and problem solving, growing persistence capability in an activity, responsibility and leadership skills, making mistakes in a safe environment, as well as the ability to recognize the acts of others are also trained and developed [3-5, 8].

The learning and cognitive empowerment through the mental game, with proper support, is a continuous process in which people of any age group can participate. The list of educational games that enact cognitive functions is great. LEDs will indicate some of the most prominent educational games used in the memory center of the Naval Hospital in non-pharmaceutical interventions.

Chess is one of the most popular spiritual games. The aim of the game is to remove the opponent's king off the chessboard through specific movements of piers (pawns). The intellectual preoccupation with the game develops and activates the inactive dendrites in neurons of the brain. This helps develop the players' concentration, communication and cognitive skills, critical and strategic thinking, memory, problem solving, intellectual maturity and creativity, self-confidence and self-esteem. It also encourages thorough thinking, exhaustive and conclusive analysis of the relationship between action - reaction - consistency and visualization sequence relationships. Additionally, it is worth noting that, while a player processes the chess positions, both hemispheres of the brain are exerted. Chess helps significantly to the development of the brain part that is responsible for strategic planning and forecasting (prefrontal cortex), which is also responsible for self-control and critical capacity [9, 10].

The Sudoku is a spiritual game that can be learned at any age. In any Sudoku game blank squares are to be filled, so that each number between 1 and 9 is shown once on each row, column and grid. Through the preoccupation with this game, careful thinking is exercised, as the above mentioned complex instructions are to be taken into consideration. Working memory and general cognitive functions are exercised, while attention, observation and information processing are also developed. At the same time, it activates sensory perception and develops concentration ability, as concentration of attention on three points simultaneously (line - column - in grid) is required. Complementary skills, such as making logical decisions and problem solving, are also improved, through experimentation of possible solutions of the game. Finally there is the individual's motivation and efficiency, while positive mood can also be created [11-13].

Another educational game that can keep the mind alert is the puzzle. The aim is the connection of the pieces so as to expose a specific image. The puzzle is a valuable help to develop eye-hand coordination while developing and training motor skills, in particular the fine motor. These are also the skills required when eating, writing and working with small objects. Puzzles help also enhance someone's visual - spatial perception, resulting in better space and time orientation skills. Puzzles and memory cards have been proved to be stimulating memory, particularly working memory, conceptual thinking and concentration. It is noteworthy that even the simplest puzzle requires that the player analyzes and uses his mind in order to put the pieces in place, which makes puzzle a very good tool in enhancing someone's problem solving ability. It is understood that with the puzzle the executive functions of the brain as a whole are trained. Additionally, communication skills are strengthened; imagination and creativity are promoted, while the player's confidence is increased [4, 5, 14, 15].

Crossword is a mind and knowledge game. The player is asked to fill in the blank boxes with the correct letters in order to form words, with the help of specific definitions. Crosswords is a broad category of different types. There are crosswords with definitions into the blank spaces or these where definitions are distributed in horizontal and vertical, while there are searchwords in which the correct words from a box composed of letters should be disclosed. People engaged in activities like crosswords achieve gain strengthened memory, improved cognitive functions, as well as enriched vocabulary. Verbal fluency and working memory are additionally improved, and therefore the expression ability and critical thinking are enhanced. Attention and observation skills also improve, as well as logical thinking. In addition, focusing skills and spatial perception of the letters in specific crossword square positions are promoted. Finally, puzzles improve the visual - spatial perception and, as observed as in all games, inventiveness and significant change of mood are also achieved [7, 16, 14].

Construction games contribute significantly to attention and observation skills, as well as to fine motor, speed and balance enhancement. Through someone's effort when dealing with this kind of games, executive functions are largely trained, including working memory, reasoning, learning, behavioral control and emotion, and verbal communication.

Moreover, additional games that also contribute to cognitive enhancement is Scrabble (word formation game), memory games with cards, labyrinths and crafts. They help enhance a number of cognitive skills, verbal fluency, visual memory, visual-motor coordination and fine motor. In conclusion, where physical exercise is intended to keep the body fit and healthy, educational games are designed to keep the mind vigilant [7, 16-19].

As mentioned above, educational games help enhance someone's intelligence and ability of concentration, practice arithmetic ability and cultivate the memory. They offer knowledge and are intended to promote intelligence factors such as rapid perception, differentiation, and identification. Numerous studies investigate the effectiveness of educational games in cognitive enhancement.

A study called "Measurable benefits on brain activity from the practice of educational leisure" was published in March 2014. It examined 60 retired people in order to compare the brain activity of the subjects, while they engaged in various kinds of recreational activities. Retirees were divided into three groups according to the different

activities in which they practiced. The first group participated in educational activities, the second group in memory games and the third group in card games. The results indicated that participation in educational activities is a useful practice to protect the brain [18].

Another research published in February 2013 with the title "Brain training game boosts executive functions, working memory and processing speed in the young adults: a randomized controlled trial" investigated the existence of beneficial effects of intellectual games in staff functions. The investigation of the effect of brain training games on a wide range of cognitive functions in young adults was examined. Double - blind randomized controlled trial was performed, using a popular spiritual brain training game, puzzles and riddles. The participants were 32 volunteers, randomly divided into two groups. Participants of all groups participated in the game for 15 minutes a day, at least five days a week, for four weeks. Cognitive tests were performed before and after each workout and included eight categories, fluid intelligence, executive functions, working memory, short term memory, attention, processing speed, visual ability and reading ability.

The results of this study showed that the spiritual brain training game improved the subjects' executive functions, working memory and processing speed in the first group of volunteers. Also, through the puzzles and riddles used in the second group, improvement in attention and visual - spatial ability was shown. The specific cognitive functions, which these spiritual games had beneficial effects on, were, according to the survey, the staff functions, the working memory and processing speed. As a result, it was indicated that the educational game could be a simple and easy way to improve some cognitive functions. The findings of this study are particularly useful for applications in educational and clinical fields [16].

A research published in June 2003 titled "Leisure activities and the risk of dementia in the elderly" studied the correlation between specific activities and lower risk of dementia. The sample was formed by 469 subjects aged over 75 years with no dementia diagnosis who lived in the community, while the age, gender, educational level, cognitive status and the presence of chronic medical diseases were recorded. The study examined the frequency of participation in activities at the start of the study. Cognitive assessment scales and physical activities were administered, and daily activities were evaluated on weekly basis.

Among the activities included were reading, board games and educational toys, musical instruments and dancing. Increase of even one degree in the test result for the control of cognitive activity was significantly associated with a reduced risk of dementia. In a follow-up period of 5.1 years, dementia was developed in 124 subjects (Alzheimer's disease in 61 subjects, vascular dementia in 30, mixed dementia in 25 and other types of dementia in 8). The study indicated that participation in leisure activities is associated with a reduced risk of dementia [19].

In northern Taiwan, a study in elderly people with cognitive impairment was published in October 2013 under the title "The effects of participation in leisure activities on neuropsychiatric symptoms of persons with cognitive impairment: a cross - sectional study". Aim of the study was to describe the indicators of activities correlated with neuropsychiatric symptoms in the population. 60 couples took part as patient-caregiver. Patients participated in about five activities, playing chess and memory cards, participation in cultural events, cruising and fishing. The results showed impairment in activities that were significantly associated with depressive symptoms. According to the researchers of this study, the results can be used by health professionals in order to design customized programs aiming to improve the quality of life of patients with cognitive impairment. It was also suggested that entertainment programs with a focus on educational activities should be developed -specially designed to meet the expanding needs of this population [9].

In March 2015 a study aiming to achieve a multifaceted approach to the prevention of cognitive decline in older people at high risk was published by the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). The title of the observational study is "A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomized controlled trial".

In a double-blind randomized controlled study participated people aged 60-77 years. The intervention lasted two years and was related to diet, exercise, cognitive training including educational games and vascular monitoring. 631 people were in the intervention group and 629 in the control group. The primary results showed change of cognitive decline resulting from the neuropsychological control (NTB). The findings from this large randomized controlled trial suggest that a multifaceted intervention system could improve or stabilize cognitive function in elderly people belonging to increased risk group for cognitive impairment [7].

The prospective study "Playing board games, cognitive decline and dementia: a French population-based cohort study", published in August 2013 was designed to study the relationship between social games and the risk of dementia. It examined 3675 participants without dementia at baseline, who were evaluated for 20 years. Among them, 840 participants developed dementia during the 20 year follow-up. The risk of dementia onset was 15% lower in people playing games of that who were not. The degree of depression in participants examined and the cognitive level as evaluated by the mini mental state examination (MMSE) were both taken into account. Persons who were playing board games had smaller decline in MMSE score and lower depression levels. General conclusion of researchers is that there is a possible beneficial effect of playing board games on the risk of developing dementia and depression [17].

Measures

The tools used for the conduct of the study is the scale Mini Mental State Examination (MMSE), the Verbal Fluency test, the Recall from Table 10 words test, the Geriatric Depression Scale (GDS).

Method

This study lasted six months and involved a total of 20 people. Distinction was made according to the mark of cognitive decline. Thus formed two groups of 10 individuals, wherein the group A had mild cognitive impairment, and the results in the range Mini Mental State Examination (MMSE) was 26-30. Group B had mild dementia and results in the MMSE scale ranged from 19 to 25. At the start of the study were administered to both groups the MMSE scale where the Group A results ranged from 26 to 30 while the B group between 19-25 [20]. Moreover given the test Revocation list of 10 words. Was given to all the participants a list of 10 words and were asked to recall all the words in the list having 3 attempts. The measurement results shown in A group average 6/10 and 5/10 B group. Then given the Verbal Fluency test, where were two elements to control the phonological fluency and 1 element for checking semantic fluency. The average of the results was in the A group 9, while in group B 8. Finally completed all participants Geriatric Depression Scale (GDS) where the overall result was an average 7 [21-24]. For the duration of 6 months following, all subjects watched once weekly sessions of one hour. The first half hour solve Sudoku and the rest half an hour playing a construction game. At the end of six months was repeated all tests.

Results

In the reassessment of the participants conducted at the end of the study, it was observed change results in scale Mini Mental State Examination (MMSE) by 2 points in both groups. Further slight improvement was observed in Verbal Fluency test by one unit in both groups. The results, therefore, in group A showed an average of 10 while in group B the average result was 9. Improvement 2 points observed in the recall test from Table 10 words. Specifically, the A group from 6/10, which was fund in the initial measurement, increased to 8/10, then the B group from 5/10 switched to 7/10. In the overall result of the Geriatric Depression Scale (GDS) after retesting conducted it declined from 7 was six months ago to 5. The results of this study show an improvement in immediate recall and concentration which is evidenced by the change in indicators. Additionally there is a change in the depressed mood of the participants.

Discussion

The implementation of empowerment group enhancing cognitive functions through educational games in the context of non-pharmaceutical intervention, conducted at the Naval Hospital of Piraeus, confirmed the objectives in a period of 6 months. This report includes more qualitative data derived from the activities and interviews before and after the study. Furthermore may the data collected to form a small sample, but the goal is to collect data from the following groups to be analyzed and statistically valid. The experience of the intervention was very positive as the need for support and intervention is very important for patients with cognitive disorders.

The educational game is the only mind exercise for men and women of all ages and contribute significantly to the behavior logic placement of mind, techniques of mind (numerical, statistical), memory and concentration [10, 16-19]. Brain games are taught internationally in schools and are part of the curriculum in several prominent universities.

Currently, at the Naval Hospital, there is increased interest for members in groups of educational games. The integration of educational game in every mental empowerment group is essential. Thus, apart from other mental exercises, teaching educational games in small groups of 6 to 8 players is a core activity. People attend engagement sessions with educational games, lasting an hour, once a week. Week after week, the group members have the opportunity to practice the games taught on each visit. Once the rules of the game have been learned and understood, the degree of difficulty gradually rises. This enables the process of learning and observation. Through the use of educational games, perception is enhanced, as well as socialization, since the group members are encouraged to interact with the other members of the group.

The authors declare that they have no conflicts of interest.

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Managing caregiver's burden through group counseling and psychoeducation

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Abstract

It is widely known that dementia has an impact not only on patients but also on their caregivers. The term "caregiver burden" refers to the physical, emotional or financial oppression that caregivers endure due to a patient's suffering from a chronic disease. **Aim:** The caregiver's support group aimed to manage the burden of caregivers of Naval Hospital of Piraeus in order to improve their psychological state and provide education to help them understand the fundamentals of the disease. **Measures and Method:** This group was composed of eight women who had fully assumed the responsibility of taking care of a spouse or a parent suffering from mild cognitive impairment. The symptoms of mild cognitive impairment were examined by Mini-Mental State Examination (MMSE) and Neuropsychiatric Inventory (NPI-12). Individual interviews for each of the participants were taken in order to record psychological history whereas depression, anxiety levels and the sense of burden were examined by using Hamilton Anxiety, Hamilton-Depression (HAM-A, HAM-D) and Burden Interview before and at the end of the therapy sessions. Additionally, the satisfaction from the relationship with the patient was measured by Burns Relationship Satisfaction Scale (BRSS). **Results:** Through group counseling and psychoeducation it has been observed that anxiety and depression levels declined (from 18-22 to 14-18 for HAM-A and from 13-17 to 9-13 for HAM-D). The feeling of burden was also decreased (from 55-60 to 50-55). Moreover it was observed that caregivers could better manage everyday practical issues concerning the patients' care and had improved their problem solving ability. The satisfaction of the relationship with the patient/ between patients and caregivers was a factor that could reduce the sense of perceived burden of caregiver. **Conclusion:** The practice of group counseling and psychoeducation in caregivers of patients with dementia in Naval Hospital of Piraeus confirmed the initials aims after the period of 12 weeks.

Introduction

Dementia is characterized by progressive impairment of memory and other cognitive functions resulting in dependence of all affected individuals and the necessity for supportive care. The majority of people with dementia has one of their family members as a primary caregiver, especially spouses who are elderly themselves. These family caregivers play an important role in supporting disadvantaged elderly people throughout the disease and are one of the main resources of the health care system. This task is not easy and is full of emotional intensity and physical exhaustion which, as a result, causes the individuals who take care of such patients to empathize with them [1]. More than half of the caregivers of people with dementia have reported to have great levels of burden coming from the caring, which is often associated with depression, anxiety, higher physical vulnerability and mortality [2].

The term "caregiver" is used to describe someone who takes care or provides support to someone who is ill, elderly or has a disability. Usually these people are close relatives, friends or neighbors. Some prefer to view themselves solely as a son/daughter/relative and do not like to be labeled with the term "caregiver". However, this term can help some people and is widely used by specialists as it helps them to separate the practice of caregiving to that of the relationship with the person who provides it.

Although there is no precise definition of the term "family care" it is generally accepted to include the kind of care that goes beyond the limits of the ordinary in family relationships. Typically, the provision of care includes investing time, energy and money for long periods. It includes work that may be unpleasant, difficult, tedious and psychologically stressful or physically grueling [3].

The first signs of impairment that may be observed by the family of the person with dementia are the difficulty of the patient to remember recent events and carry out daily routines. The person may also exhibit confusion, changes in personality or behavior, limited judgment, difficulty in finding the right words, completing thoughts or follow instructions. Initially the family denies the diagnosis of the disease and finds it difficult to accept that fact. They underestimate the symptoms of the disease, are led to a constant rotation of doctors and seek alternative therapies. But as the disease progresses, the family is forced to make a major effort to meet the caring responsibilities of the affected family member, despite the difficulty to face their own feelings of pain and grief for their beloved one.

Generally the families who act as caregivers to patients of dementia experience increased physical and psychiatric morbidity, low quality of life and social isolation [2-6]. The accumulation of problems arising from taking care of a dependent family member is usually referred as "burden" [1,6]. Given the specific nature of the disease, caregiving people with dementia appear to be more difficult and burdensome than caregiving people with other chronic diseases. A patient suffering from dementia is in need of special treatment in matters of personal hygiene, dressing and diet. As their behavior is constantly changing, they become more reckless and aggressive and less able to perceive danger. The stress and frustration experienced daily as well as depression are significant enough to change the whole personality of the patient. Delusions, hallucinations and insomnia are important symptoms that

the caregiver should be aware of.

As time passes by, these people find it difficult to take care of themselves even in fundamental aspects of everyday life and become more and more dependent on other family members. The family member who has the role of the caregiver needs to find a way to provide help in a series of everyday problems such as difficulties in dressing, eating, or more complex, such as using the toilet and taking a bath, mobility difficulties and dysfunctional behavior. These problems cause more discomfort to patients and their families in contrast to the deterioration of memory or other cognitive functions and functional independence, and significantly regulate the provision for institutionalization of the patient. Compared to the general population, caregivers coming from the family environment are reported to feel emotions of hopelessness three times as much. They often report insomnia and decreased energy. Usually, they feel physical stress, social isolation, loneliness, anger, frustration, and loss of patience.

In addition there seems to be a correlation between the occurrence of behavioral and psychological symptoms and elder abuse which can be explained by the fact that these symptoms can cause certain negative reactions to others and mainly to the caregivers. Apart from the specific problems of the patient, the specificity of care of patients with dementia is also due to individual characteristics of caregivers which reported as follows [7].

• Persons who provide care (particularly spouses) come from an age group of which the population is growing rapidly and is facing an increased risk of disease.

• The experienced stress is chronic and persistent due to the progression of the disease and the patient's life expectancy that can reach many years.

• Spousal caregivers are particularly vulnerable because they lose the companionship of their spouse and this may worsen the physical and emotional problems.

• The combination of loss, long-term stress and biological vulnerability can reconcile the natural functioning of certain caregivers and increase the risk of further health problems.

• The possibility that the caregiver may get sick is connected with their decision to institutionalize the patient.

The patient-caregiver relationship that has been built during the years before the onset of the disease plays an important role in the extent of burden that the caregiver will feel during the caring period. In particular, if we take the example of a couple where the wife is playing the role of caregiver and examine the history of the couple, we will realize that low marital intimacy and unresolved interpersonal issues, that may exist, result to an increased sense of burden on the part of the wife [8]. Sometimes in fact, the previous "bad" relationship between the caregiver (whether spouse or adult child) and the patient can push the caregiver to report symptoms exhibited by the patient as being more serious than they truly are.

On the contrary it is found that the satisfaction derived from pre-existing patient-caregiver relationship can make the caregiver feel less burdened, which improves the capability of the caregiver to provide effective support and communication with the patient. Moreover, caregivers who experience low levels of satisfaction from their relationship with the patient tend to adopt poor behaviors towards them and sometimes can cause violent episodes [9]. The quality of marital relationships during the care giving period consists another issue which has already been discussed. The more positive assessment on behalf of the caregivers concerning their current marital relationships, the lower are the ratings of the burden and the sadness they experience [10].

Studies have shown that the marital relationship between patients and caregivers constitutes a protective factor against the institutionalization of the patient and can be accounted by the emotional bonding of the marital couple [11,12]. Research has concluded that marriage becomes stronger and more positive as the couples approach the senile stage of their life and they exhibit less negativity and more tenderness [13]. However, after the diagnosis of dementia, married couples go through an adjustment period and 6 months later many spouses refer that the comradeship with their husbands has changed into disruption and loss of intimacy. Due to memory and behavior problems, which are typical of dementia, many caregivers claim that the greatest challenge is communication with the patient [14]. Gallagher and Thompson studied the relationship quality between the couples (with one member suffering from dementia) employing many different ways of research, including direct filming observation, while other couples without the care giving necessity were being observed [14]. Results showed that despite the continuing impairment of the disease, certain elements of communication between the couples with long term marital relationship have remained intact, especially during pleasant activities and experiences, such as having lunch. On the other hand it was found that women who had the care giving role were less resilient, showed less reciprocity and reported less mutual enjoyment.

In a research concerning the burden in regard to the affinity degree [15], a significant difference between the spouses and the daughters was found. Spouses who were living with the patient reported a higher degree of burden due to the symptoms of disorientation and the problems in the everyday activities. The daughters, however, were affected by a variety of variables regarding the cohabitation conditions, while in cases where the patient was living in an institution, the daughters were affected by the long term stress of care and the rapid impairment in the patient's condition.

Other studies which have come to the conclusion that the daughters experience greater burden than the spouses, support that the role of care is expected on behalf of wives for their husbands. Many spouses have reduced their obligations and perhaps they anticipated that they will take care of their husbands, while the daughters feel greater disruption in their lives in order to be able to respond to the role of care [16]. On the contrary, marriage was found to act as a shield against stress of care, because married daughters report that they receive greater support and show less depressive behavior in comparison with daughters without a partner [17].

In the family context, the challenges faced by the caregiver burden in physical, psychological, social and economic level [18]. On the physical level an increase in the occurrence of chronic diseases (hypertension, arthritis, diseases of the immune system), greater use of tranquillizers and antidepressants and more frequent hospitalization can be observed [19,20].

The psychological burden of caregivers is also greatly increased. It has been observed to exhibit clinically significant anxiety (10-35%) and depression (10-34%) [21]. Concentration loss may also be observed as a result of depression or regardless of that, making caregivers unable to cope with everyday goals.

Caregivers feel frustration and disappointment because they are unable to change the course of the disease. Feelings of disappointment and frustration usually lead to irritability and anger. They feel anger because they are the ones who must provide care; other family members are usually reluctant to help and patient's behavior is becoming progressively more difficult. As a result, the caregiver experiences feelings of guilt about the way in which he/she behaved in the past towards the patient; about the feelings of anger he/she currently has towards him because of his eccentric, due to dementia, behavior; about the outbursts and generally the loss of self-control during the care period; about the occasional renunciation of patient-care duties; about the time spent on personal needs; about delegating part of patient-care duties to a third person. As a result they gradually tend to neglect their own needs and often lose their identity (role confusion). Sometimes caregivers report suffering from insomnia caused from patient related concerns. Thoughts such as what will be the future of the patient, whether they may get lost when going outside etc., are indicative of the stress they experience.

The social relations of the caregiver can also be greatly affected because of his involvement with the patient. His free time becomes more and more limited and as a result he starts to neglect social interaction. In case depression has made its appearance, loss of interest to social activities can be observed resulting in social isolation of the individual. From financial perspective, the caregiver faces great stress as he/she covers a wide range of costs for the patient such as, pharmaceutical, medical and hospital care, emergency nursing or house-care services as well essential equipment for the patient (e.g. special bed, wheelchair, etc.).

All of these factors together have an impact on the caregiver's quality of life which worsens over time especially when one considers the magnitude of the change taking place in his everyday life. Because of the patient's condition the caregiving is very demanding and stressful. In many cases the caregivers feel isolated, lost inside their minds, because of the burden they feel treating a disease unfamiliar to them which is aggravated daily. They see their loved one becoming increasingly distant and stranger. Thus, the caregiver lives a more degraded everyday life since it he no longer exerts essential activities for personal development and growth. In several cases he wanders aimlessly, not realizing what he wants to do and not knowing how to accommodate his own personal needs. He willingly talks about the daily problems he is facing and feels intense inability to find solution. One of the important reasons of his weakness is the lack of information on the evolution of the disease. From the caregiver's perspective, any new change in the behavior and health status of his beloved one is perceived as something unexpected.

The caregiver's psychoeducation is one of the most important tools we have at our disposal in order to help him cope with the demanding and grueling process the caregiving a patient with dementia. Psychoeducation refers to the education offered to individuals with a mental health condition and their families to help empower them and deal with their condition and the factors that are inextricably connected with it. Education for providing care to patients with dementia is very important from the beginning of the disease. Its significance lies in providing information to the caregiver and the patient regarding the disease, its symptoms and its course and progression as well as the special care that is required. Through this education the caregiver is able to realize that the quality of care is affected by his psychological state. The patient may not be able to fully understand what is going on around him, however, he is able to feel the anxiety, the nervousness and stress, something that may make his condition even worse.

The caregiver is faced to cultivate specific skills which will briefly examine. Firstly, from the day of the diagnosis and during the disease the caregiver will come across various changes that will have to manage. These changes take place within the family of the patient due to the lifestyle change of the family members and especially that of the caregiver, The latter is sometimes forced to quit his job or waive personal dreams and ambitions in order to devote himself to taking care of the patient. Furthermore reversal of family roles occurs, a fact that complicate both the caregiver and the patient up until these new roles become familiar and clear within the family members. It has been observed that the cognitive restructuring of the emotional background of the word "care" can reduce the sense of burden on the part of the caregiver. Thus, if this word is linked with concepts such as love, pleasure or blessing, positive emotions will arise and as such the caregiver will experience a reduced sense of burden resulting from the patient caregiving.

On a second level the caregiver is faced to manage any tensions that arise within the family because of the new roles and responsibilities. In the case that the spouse is the one who takes the role of the caregiver, other responsibilities such as guarding grandchildren obstruct her or her children who may react because she can no longer accommodate them. In another case where the daughter is the caregiver and the patient is the parent, her husband may strongly her new role will have an impact to their daily lives. Thus, the caregiver is asked to find the balance, to vacillate between conflicting interests and responsibilities which adversely affect his psychological state. The allocation of roles and responsibilities is something that can relieve and encourage family members to adjust to the new reality [22].

Research findings show that interventions which include providing support to the caregiver alongside with education related to the particularities of the disease are much more effective for him than those including solely support. The psychoeducational interventions are therefore found to be more effective as to reduce depression and burden sensed by the caregiver [23,24].

The benefits which caregivers have by participating in these groups include the relief they feel by being with people who have similar experiences and feelings, the emotional support they feel from others, the ability to solve problems, the information they receive about the caregivers' network and the skills they acquire which are necessary for a caregiver [25]. Through support groups the caregivers have the opportunity to normalize reactions related to the disease. They realize through discussion with other people who provide care to a person suffering from dementia that the feelings of anger, distress, fear, guilt and other emotions that cause impairment are expected to be experienced. Moreover they realize through the group that they are not alone; that even the most bizarre behaviors and situations are normal to take place due to the particularity of the disease. Even their own approaches to the patient, though they might seem irregular to others, are heard as normal and acceptable through the group. This continuous encouragement and support provided to caregivers through the group have often been the reason for extending the caring ability of the caregiver. This is due to the fact that the support group is a great place to share tough emotions such as anger, fatigue, sadness and frustration without feeling shame or guilt. The group creates a special place where the caregiver feels safe to express his frustration towards the family and professionals who do not live with expectations or standards. A place where feelings of failure when things go wrong are nonexistent and most importantly where participants share new caregiving techniques or learn to be able to control their emotional responses with a more constructive way.

There is always the possibility for caregivers to refuse to be a part of a support group. The reason is that the caregiver himself may not recognize his status as a caregiver or resist to be labeled as one. The reason a person may not recognize this property or his denial of being the caregiver even though he knows it is the sense of duty felt by family members towards the diseased member. Moreover within a married couple the one who has the role of the caregiver may feel betrayal towards the other part when thinking of joining such a support group. They feel ashamed to express and share their feelings with other people. Men tend to consider that joining a support group is something that women do. An important reason for refusing involvement to support groups can be the fear felt by caregivers for the estimates regarding the course of the disease. There is also the possibility that the caregiver feels that no one can replace him in the role of providing care and can feel great amount of pressure making him to think that he has no time to spare to such activities. Finally, many caregivers feel that no one can help or understand their tough position and refuse to participate in support groups.

Last year a support group for caregivers begun to operate in the memory disorder center of the Naval Hospital of Piraeus. Due to the large influx of patients suffering from dementia, the need for support and education of these precious relatives was more than clear. The vast majority were women, more often wives and sometimes daughters of the patient. The everyday life of these people had changed greatly; they were under immense pressure, focused exclusively on how to help the patient, but were missing the part of thinking about their own health and condition.

When the support group initially started its operation, its members were often stressed because they were away from the patient, fearing that they may get lost or need them. In order to relief them from this we formed the group program in such a way that the patient participated in the cognitive empowerment group while the caregiver was involved in the support group, minimizing that empty time that could cause practical difficulties for the patient and the caregiver. Gradually both sides were able to overcome this stress to a large extent.

The caregiver's support group aimed to manage the burden of caregivers in order to improve their psychological state (stress levels and depression) and provide education to help them understand the fundamentals of the disease, making them more effective when dealing with the patient on all levels of the disease.

Measures and Method

The group of caregivers consisted of eight women who had undertaken entirely the care of the person with dementia who was either spouse or parent. All participants were women and caregivers of people with mild cognitive impairment. The patients were been examined by MMSE (with total score 19-24). The counseling and psychoeducation group included 12 sessions (one session per week) and was divided into thematic sections. Initially HAMILTON-ANXIETY (HAM-A) and HAMILTON-DEPRESSION (HAM-D) questionnaires were distributed to the members of the group in order to assess the levels of anxiety and depression. The levels of burden were measured through Burden Interview (ZIP) and the levels of satisfaction from the prior relationship with the patient were measured through Burns Relationship Scale (BRSS) [26,27]. Neuropsychiatric Inventory NPI-12 was administered to caregivers. At the same time interviews with the participants took place in order to record the psychosocial history.

The group sessions were divided into three parts: the first three were devoted to the acquaintance of the members, to educate the members regarding the condition and its consequences on the patient's health, and to provide forms with instructions and information. Caregivers were involved in various activities inviting them to introduce themselves to the group and talk about their relationship with the patient.

Thence, through the information material which was extensively discussed within the group, the members

were asked to familiarize themselves with the disease and discovered similarities between patients. In the following five sessions, through structured activities and provided material, they were given space to express all their emotions. The largest part of the material, which was used, came from structures activities designed to promote group expression and communication, which aimed at:

- Emotional expression (acceptance of “not positive” emotions)
- Communication within the group
- The improvement of connection with the patient (memory recollection)
- Processing grief and loss
- The enhancement of personal care in every level (physical, psychological, social etc.)
- The pursuit of help and support from the family and social environment.

In the last four sessions, short-term objectives were given to the members where each individual tried to accomplish until the next session and share their experience throughout their efforts with the rest of the group. The objectives were patient behavior management, solving practical issues, personal relief during a day with specific free time, seeking help from other family members or institutions etc.

Upon completion of the group questionnaires to the participants were administered once again as well as personal interviews aimed to record their experiences. Below, psychometric tools are summarized.

The **Hamilton Depression Rating Scale (HAM-D)** was published by Max Hamilton in 1960 and was designed to measure the severity of depression in hospitalized patients already diagnosed with major depressive disorder. It contains 17 items to be rated from 0 to 4 resulting to a total score range of 0-50. The item rating is based on the symptoms reported by the patient during the interview, the assessor's observations and information collected by third parties (relatives, nurses).During scoring procedure there is no distinction between the intensity and frequency of symptoms, but these two should be borne equally by the appraiser's judgment. The scale covers the patient's condition during the week preceding the scoring regarding most symptoms except sleep disorders related to the last three days. Assessment time is estimated between 15-20 minutes.

The **Hamilton Anxiety Rating Scale (HAM-A)** is a psychological questionnaire used by clinicians to evaluate the severity of the patient's anxiety. Although he was one of the first anxiety rating scales to be published, the HAM-A remains widely used by clinicians. Though it was one of the first anxiety rating scales to be published, the HAM-A remains widely used by clinicians. The scale consists of 14 items designed to assess the severity of the patient's anxiety. Each of the 14 species contains a number of symptoms, and each group of symptoms is graded on a scale from zero to four, with four being the most severe. All these results are used to calculate an overall score that indicates a person’s anxiety severity.

The **Burn Relationship Satisfaction Scale (BRSS) [3]** is a self-administered questionnaire consisting of seven items designed to measure the satisfaction in various areas of the relationship. It identifies the degree of relationship satisfaction and considers communication and availability, conflict resolution, the degree of interaction and interest, intimacy and closeness, satisfaction coming from the roles within the relationship and general relationship satisfaction. The respondent reports the degree of satisfaction in each of the items on a scale from 0 (not at all satisfied) to 6 (very satisfied). Total scores range from 0-42, with higher scores indicate high satisfaction.

The **Zarit Burden Interview (ZBI) [27, 28]** is a psychometric tool composed of 22 questions, which measures the level of psychological health, emotional, well-being, social and family life, the finances and degree of control over one’s life. Each item on the interview is a statement which the caregiver is asked to endorse using a 5-point scale. The total score ranges from 0 (no charge) to 88 (very high cost).

The **Neuropsychiatric Inventory (NPI-12)** has the purpose to obtain information on the presence of psychopathology in patients with brain disorders. The NPI was developed for application to patients with Alzheimer’s disease and other dementias, but it may be useful in the assessment of behavioral changes in other conditions.

Results

Through group counseling and psychoeducation it has been observed that stress and depression levels declined (from 18-22 to 14-18 for HAM-A and from 13-17 to 9-13 for HAM-D). To feeling of burden was also decreased (from 55-60 to 50-55). In addition through NPI-12 was observed on average anxiety (frequency 1, severity 2, distress 4), irritability (frequency 2, severity 2, distress 4), aberrant motor behavior (frequency 2, severity 3, distress 5), sleep and nighttime behavior disorders (frequency 1, severity 1, distress 3) to patients. These symptoms were very stressful for the caregivers. Through group counseling and psychoeducation caregivers could better manage everyday practical issues concerning the patient and had improved their problem solving ability. Now the patient's behavior did not seem incomprehensible because the group had been informed of the condition and knew what to expect to some extent. Emotional expression was more thorough especially after the fifth session. As soon as an atmosphere of trust and acceptance was created within the group, these women were now able to express their ambivalent feelings, admitting their anger related to the patient's behavior and at the same time their excruciating guilt for that exact feeling. There was a great relief on the part of each individual when they started to realize that they were feeling the same way with the rest of the group, a fact that furtherly enhanced the emotional expression. Caregivers were able to undercut the high expectations they had of themselves with respect to the energy they had to devote to the patient, and were able to set more realistic and reasonable goals.

Moreover the caregivers were able to get in touch with the past-self of the patient, could retrieve memories from his past activities and his past, before dementia, way of life. Through a collage made by each individual within the group, we asked them to put a picture of their beloved one who is now sick in the center of the collage and they found pictures associated with his personality and preferences. Afterwards they shared this collage with the rest of the group, and talked about their beloved one, mourned for how he changed, and received understanding and support from the other ladies. At the end of the group sessions, during the individual interviews, the majority stated that this activity had touched them inside, enabled them to see the patient with leniency and feel more positive emotions towards him. One of the ladies reported that in many cases the images of this collage were passing through her mind as she was taking care of the patient, and this gave her a pleasant character in the caring process. Furthermore, the participants resocialized through contact and sharing with the other members. They admitted that they had been detached from their social environment due to the irregular behavior of the patient and from a point and after they started to feel guilty to go without the patient. At the end of the sessions the members of the group kept in touch, bonded and had time away from the patient's house, shifting some of the responsibility of care to other family members.

Thus, the past good caregiver-patient relationship was observed that is indeed a good predictor that reduces the feelings of burden that the caregiver could feel. Some caregivers admitted that their relationship with the patient was not good years before dementia occurred, sketching difficult aspects of his character (three cases in marital relationship and a case in parenting). These caregivers recorded the highest levels of depression and burden within the group.

Progress was observed within the group, which lies on the ground that three members were able to ask for help concerning the patients' care from the rest of the family. They were women with a high sense of duty and self-sacrifice attitude, who were led to emotional burnout. Through role-playing and encouragement they could ask for help from other members of the family. This led to delegation of work, even if it was partial, and resulted in the tangible relief of the specific participants.

Finally, it was observed that a good relationship with the supervising doctor consists an important motive for the caregivers in order to participate in a group intervention. Most of the ladies, who took part in the group, reported during their initial interview that they were doing so because their doctor has asked them to, considering that this will help them. It was not obvious that they had realized either the real benefits or what would be included in the group sessions. However, doctors' opinion was proved to be the driving force in order for these women to agree to participate. After the completion of the program, of course, they were asking when there will be organized another group so that they can participate again.

Discussion

The implementation of group counseling and psycho-education on the caregivers of people with mild cognitive disorder in the context of the memory centre of Naval Hospital of Piraeus confirmed the goals of the program in just 12 weeks interval. In fact, this year there is an active similar group and there is an increased participation interest for one more until the end of the summer.

Although our data were gathered from a small sample there is the goal to collect data from the next groups in order to be statistically analyzed and valid research data to derive from this process. The present report includes more qualitative data which derived from activities within the group and from the individual interviews before and after the intervention. A significant limitation of this study regarding results' exportation was the fact that the group did not include men.

The experience we had from materialization of this intervention was very positive. The need for support and briefing is particularly important for the caregivers, even though they try to hide it. The patient is undeniably on the front line due to the diagnosis and the necessity of monitoring dementia. However, if we do not have calm and healthy caregivers, then the patients will not be able to receive the proper care for themselves.

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The effect of day center on life quality of dementia patients

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Abstract

Dementia constitutes one of the greatest medical and social challenges of our era. Dementia includes an aggregate of psychosocial, diverse factors, that tend to affect the mental balance and the life quality of the patients as well as their provisors. The achievement of balanced mental health can be succeeded through the consolidation of mental formation in the individual and the detection of its capacity degree to think and operate with integral clarity. Respectively, the life quality is achieved by the preservation and development of social interactions of the individual, but also through the existence of sentimental and spiritual life. The day center through an action plan, which is structured in small groups, includes on the one hand the mind empowerment, on the other hand the mental invigoration. Non pharmaceutical healing approaches are organized through art, speech therapy, occupational therapy, educational games as well as memory enhancement exercises. In this way an educational frame is being created where the participants socialize, evaluate themselves and amplify their ability of expression, stasis and behavior towards everyday issues which may appear. An important portion of patients needs is being covered, such as the most natural life, the organization of the daily routine, the simplification of lifestyle, but also the tolerance of the particularity that expresses them. In parallel the emotional needs are being recognized and covered while simultaneously lucrative ground is created for spherical information and proper per event support and counseling of the surrounding.

Introduction

Dementia is a disease that gradually reduces mental capacity thus reduced and the capacity of the individual, even before the official diagnosis, which is usually performed in mild stages. The cognitive functions affected include general mental competence, learning ability and memory, speech, attitude, perception, concentration, judgment, problem-solving and social role. It is a syndrome that can be caused by a number of progressive disorders that affect memory, thought, behavior and the ability to perform daily functions.

The forms of dementia are evolving degenerative disorders of the brain and not a normal consequence of aging, which means that prevention is possible. Proper care can improve the quality of life of patients and their families, as well as the specificity of the disease adversely affects the areas of social and professional daily life, causing a progressive decline in the skills of hand, while tiered charge of it.

One definition, which has been formed for dementia, claims that the disease is an acquired and persistent reduction of mental abilities, which affects multiple cognitive domains, and is serious enough to pose a problem in everyday, professional and social life of the individual [1-3].

Quality Of Life

Since the time of Aristotle (384-322 BC) was confined the need to designate and label the quality of life: The philosopher proposes in the Nicomachean Ethics "bliss" as the most important asset and as the ultimate purpose of human life, which equivalent to the *"good life"* and *"well-doing."* The practice of virtue, according to Aristotle's teaching leads to bliss, which is art and is achieved by a behavior that characterizes the order and harmony, stability, consistency and coordination, ie *by nature* and *flat aretin living.* It argues that "happiness is a kind of mental energy in the measures of perfect virtue".

The term quality of life is a concept that over time developed and became more complex. To date there is no commonly accepted definition of quality of life, especially as the concept is the boundary between the humanities, social sciences and health sciences. The quality of life is considered a personal experience, the dimensions of which are different in each. This is a subjective definition, which is shaped by the experiences and aspirations of each individual. Apart, however, from personal experience, quality of life is a theoretical concept. Defined research, measured and interpreted statistically, and may employ a variety of disciplines such as medicine, psychology, sociology, architecture, urban planning and economics [4-6].

There is no consensus as to the definition of quality of life, but most researchers concur that the concept is multidimensional and includes overall satisfaction a person feels his life combined with a subjective sense of wellbeing and enjoyment, often measured as physical, psychological and social. The quality of life associated with the satisfaction that draws a person through objectively defined his life factors. Partly influenced by his study of satisfactory activities in his spare time and the subjective perception of the degree of functionality in important areas of life. On a theoretical basis, the quality of life can be defined to describe the characteristics, circumstances or areas of life that are necessary for the functioning of individuals as independent and autonomous beings.

According to the aforementioned quality of life is the degree of enjoyment and realization that people derive from their lives in the context of economic, cultural and other conditions. It is also the degree to which a person enjoys the important possibilities of life. These features are the result of the opportunities and constraints that a person has in his life and reflect the interaction of personal and environmental factors. This freedom of action make sense operations, professional and family prestige, integrity and performance of biological and psychosocial function in their daily life and health maintenance. It is simplified, the good life situation as consisting of two players the ability to perform the patient daily activities that reflect physical, social and mental strength and satisfaction in terms of functionality.

The World Health Organization (WHO) in 1995, its quality of life as "The subjective perception of the person's position in life, which formed the context of the values and cultural characteristics of the society in which he lives, and is depending on personal goals, expectations, criteria, interests and concerns. This is a broad concept that includes a complex way physical health, psychological state, level of independence, social relationships, personal beliefs and salient features of the environment. "The definition of quality of life, however, is intimately connected with the personal and purely subjective context in which it is addressed [7-9]. Scientific research has shown that quality of life is measured using weighted questionnaires which evaluate the biological, spiritual and psychological factors underlying quality of life consists. To facilitate these measurements are set appropriate indicators have resulted from systematic and scientific study and considered valid.

The indicators are divided into two categories based on the true objective and not subjective nature:

Objective Quality of Life Indicators:

- Health
  - Pain and physical complaints
  - Energy vs fatigue
  - Sleep and rest
  - Mobility
  - Activities of daily living
  - Dependence on drugs and therapies
- The natural environment
- The space and living conditions
- The availability of time
- Social activity
- The balanced employment status
- The economic capacity to cover basic needs

Subjective Quality of Life Indicators:

- Esteem levels
- The perception of body image and appearance
- The thinking, the mood for learning, enhance memory and concentration
- The reported life satisfaction
- Positive feelings
- The feeling of competence and satisfaction with the functionality of the individual in different areas of life
- The intellectual interests and personal beliefs
- Personal relationships
- Support from the immediate social environment
- The satisfaction with the services provided
- The opportunity to participate in various social activities

The ages that show advanced cognitive deficits, mostly belonging to the third age. Factors that tend to affect the appearance of cognitive disorders in the elderly age, educational level, loneliness and physical diseases that already spans in life. Participants in cognitive empowerment programs have some social standard platitudes. Showing socially isolated, which is largely due to the sense of imbalance parameters of their everyday life, combined with the natural sense of insecurity which occurs incrementally increasing with age [1, 5,10,11].

Day Centre

The aim of the Memory Day Centre is the organization and implementation of group and individual treatment programs for people with dementia on the one hand and comprehensive information, education and per event maximum psychological support of relatives of people with dementia on the other hand. The duration of the programs and activities selected are adapted to the specific needs of each patient. Main goal of cognitive empowerment programs is to stabilize cognitive function of demented patients. Mental empowerment programs utilize existing mental capacity of patients through a series of exercises, such as: orientation in space and time, relearn material through appropriate techniques, exercises to improve memory, attention, speech, abstract thinking etc. The Memory Day Centre creates groups that are separated depending on the stage of the disease, deficits in cognitive and educational attainment levels. Along the way the programs are expected to stabilize and gradually improve certain cognitive functions. The contribution of these programs in motivating patients to improve their mood and their socialization.

Groups at Naval Hospital divided by maximum number of persons commensurate with the level of participants. In mild cognitive deficits number range 8 to 10 per group, while groups have increased deficits, the number is reduced proportionately in 5 to 8 people per group. The coordinating groups borne by health professionals, who in collaboration with the neurological clinic, categorize and offering similar exercises aimed at the gradual emergence of stabilization and improvement in neuropsychological testing. Clusters are formed once a week at the Naval Hospital in Athens and also once a week at the Naval Hospital of Piraeus. The total number of people involved and serviced by the action of outpatient clinic and co-volunteers, exceeds 90 each week, and two hospitals. Alongside cognitive enhancement provided, organized by their respective specialties, physiotherapy departments, occupational therapy and speech therapy, people who judged prudent to participate.

Mental strengthening exercises include attention, such as copy shapes, perception and speech, as the categorization exercises and matching surnames - nouns, attention exercises, such as completing proposals and squares shaded and crisis exercises, such as finding the question if it is given A number of responses (eg: given the answer "The traffic warden" and sought appropriate question like, 'Who is responsible for the smooth movement of cars? ").

Portions of physiotherapy, occupational therapy and speech therapy the day center at the Naval Hospital of Piraeus, apply therapeutic methods aimed at reducing the negative symptoms of the disease, where encountered. Through physical therapy seeks to preserve the motor skills of patients and their independence for as long as possible. With this process, the evolution of the kinetic impact is limited resulting in a qualitative increase in the daily lives of patients. The occupational therapy department focused on preserving as much as possible, self care of the individual through education both itself and carers in completing everyday activities with the active participation of the patient. The training begins after a comprehensive assessment, which aims to collect data on the appearance of man, his behavior, the level of consciousness that is, to direct, visual and auditory ability, memory, degree of articulation and understanding of language, critical ability, the ability of problem solving, thymic and its environment.

The aforementioned activities are housed in specially designed rooms, recently renovated, with easy access. Patients and their carers, following the advice and guidance of neurological clinic, following their verification, directed either to cognitive empowerment groups either in the previous sections, according to the identified needs. Can the parties to participate in all the facilities of the day center, as the curriculum and hours have been configured accordingly so that there is an imbalance and annoying waiting beyond normal.

An important aspect is also the awareness of the community on issues related to dementia. Identifying the social needs of the affected population and educating the public to become familiar with the problem. Providing educational seminars throughout the population and health professionals. The hitherto lack of awareness and understanding has resulted in inadequate preparation towards the upcoming crisis. Worldwide, the attention given to the rapidly growing problem is limited so that the majority of patients today suffer without help and without hope.

New information and communication technologies minimize distances and improve access to information and services. The information society can enhance social cohesion and to expand the capacity for full participation of citizens in every area of social and economic life and to reflect on the creation of an inclusive society. The information society must be at the service of people and is used by them to pump all of the power is the core of the information. It is natural, therefore, not understood the information society without the concepts of democracy, equal opportunities between men and women - of all ages and social stratification. The quality of life of patients with Alzheimer's disease and other dementias can be upgraded. Very often, patients, families and carers lack the support they need and deserve.

Dementia and Quality of Life

In dementia is found a set of symptoms, which tend to adversely affect the quality balanced life of affected. The progressive decline of memory is the most common, but there are also functional impairment, personality change and disturbances in behavior.

The concept of cognitive impairment included cognitive functions of memory, attention and executive functions. The attenuation in each of these cognitive processes can have devastating effects on daily functioning of people with deficiencies. Even small changes in the ability for someone to watch the information, processes it and act based on them, can have significant effects on the efficient coverage daily needs.

The day center is focused in the fields wear and initially seeks to stabilize and secondarily maximum improvement. Health professionals after observation, and cooperation with the patient himself, and with the relevant environment, record, study and adapt interventions per case. Behavior is evaluated, achieving conservation of particular identity, expression of feelings and the mood in the team and participate in the activities at regular intervals, from the entrance of the patient in mental empowerment groups, and recorded any changes arise, either negative or positive. Health professionals are invited to consider, after discussion of the Panel, in which areas new approaches and what techniques mental strength required show visible results in the individual patient [12-16]. The spiritual activities, taken together, cover a wide range of above mentioned fields. Adult participation in cognitive empowerment groups, as well as monitoring occupational therapy programs, physiotherapy and speech therapy, where necessary, tend to enhance socialization levels and cohesion among members. Diversity and personal perspective of the participants lead to positive base effects, mainly in advanced groups, which thus participate in the long run.

It has been studied that the elderly with the strongest circle of close friends, live longer than those who had fewer friends. This conclusion emerged from epidemiological research conducted in Australia in 1500 elderly over 70 years. Monitoring participants lasted for about 10 years. The aim was to explore the role of social, economic, environmental and psychological factors on health and quality of life. The beneficial effects of network friends in increasing its service life, maintained throughout the decade that the investigation lasted. According to the researchers, there are physical and psychological components of the phenomenon. From physical standpoint, friends encourage older people to eat better, stop smoking, avoid alcohol abuse and exercise more. But there are psychological beneficial effects of close friends. People need to feel connected to others. They need to feel that their life has meaning, that they have a purpose. So the network of close friends, have a major psychological impact on the elderly. Strengthens the feeling of self-confidence, improves mood, removes depression and provides energy in difficult times. It is therefore necessary to create the conditions for the elderly to create new friendships and continuously maintain their existing ties. Similarly, the society as a whole, should contribute to and strengthen the elderly can have and maintain social friendship network that benefits [17-21].

Conclusion

The forms of dementia, as well as most chronic diseases, delete a course of many years, often gradually deteriorating without the possibility of cure. The patient need, and their carers, to guarantee as many years of quality life, is undeniable. The planning, investment and cooperation in this area is crucial for both scientific research and control the social costs of these diseases and to offer hope, dignity and quality of life for millions of sufferers and their families. Through the day center, the patients who have an active role in achieving the organization of a continuing education framework in most adult lives, which in the course of planned groups, increases cognitive reserve and achieves stabilization of the mental level while improving appearance over time.
It is of significant importance now, taking into account the rapid increase of life expectancy, creating installations and structures which would allow both patients and their families, and health professionals to interact and collaborate in seeking to achieve optimal mental health and maintaining a constant quality of life.

The authors declare that they have no conflicts of interest

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Physical therapy in patients with dementia and healthy elderly using interactive games

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Keywords: Dementia -Elderly person -Interactive games

Abstract

As interactive games is out games that require movement and physical activity by the user. Interactive game are used by: Physiotherapists, occupational therapists and psychologists. The equipment which is necessary for the realization of interactive therapy are: a TV or computer, a camera placed over the screen to understand the movements of the patient, an arm and placed in the hand of the patient. We selected bibliography with interactive games wii, because the wii using verbal and visual commands integrate the patient to physical activity. We chose to present interactive games wii, because the wii using verbal and visual commands to integrate the patient in physical activity. The advantages of interactive physiotherapy aims at the development of physical condition of the patient. Results: In patients with dementia motivates giving verbal commands and physically to participate in activities and improve their concentration and improve balance. In healthy elderly people contribute to improving the balance of the first session as well enjoyable gaming application. Conclusions: The use of interactive games is safe naturopathy through adjusting deficits patient in interactive game.

Introduction

Dementia is a condition in which helps a gradual, insidious and continuous loss of cognitive ability. There are various types of dementia have different types of symptoms may experience difficulty in making sure diagnosis of a particular type of dementia. There is also the added problem of the loss of cognitive ability by increasing age. Larger diagnosable dementia are: dementia Alzheimer type, vascular dementia, Dementia due to HIV, dementia head injury, dementia due to Parkinson's disease, dementia due to Huntington's disease, dementia disease pick, dementia disease Creutzfeldt-jakob, dementia due to other general, medical conditions, substance-induced persisting dementia, dementia due to multiple etiologies, dementia not specifically determined.[1]

Possibilities deficit memory

• An inability to recall autobiographical information from long-term memory is the main feature of the disease and one that occurs early in the development of the disorder
• Impaired recall of previous learned information and sometimes memory for annoiologikes or factual information.
• Man begins to forget
• Attenuation manifest memory
• Impairment of short and long term memory
• Tendency to a shortage phenomenon but exhibit the phenomenon of temporal proximity in which the patient more accurately remember information of the end of a list spite from the beginning.
• Intervention by the previous information when learning new material
• Impairment of attention and working memory
• Attenuation semantic reflection inability memory already known information
• circumlocution and paraphrase mistakes
• Attenuation delayed memory - this appears to be best to distinguish patients with DAT than healthy[1]

Causes

Age and family history are risk factors for AD. As you get older, the risk of developing AD increases. However, the development of Alzheimer's disease is not a part of normal aging. To have a close blood relatives, such as brother, sister or parent who developed AD, increases your risk. The also have a specific combination of genes for proteins that seems to be abnormal in Alzheimer's disease, also increases your risk. Other risk factors which are not as well documented include: Long-term hypertension. Head injury History. Gender female

The cause of AD is not entirely clear, but are thought to involve both genetic and environmental factors. The diagnosis of AD is made when certain symptoms appear, and ensure that there are no other causes of dementia. An experienced clinician can diagnose Alzheimer's with certainty up to 90% by combining diagnostic tools at his disposal. Clinical, neurological and psychiatric evaluation complement Investigations control (microbiological tests, brain imaging, identification markers in cerebrospinal fluid, genetic testing) and specialized neuropsychological tests (tests of memory and other cognitive functions.

The only way to be sure that someone has AD is to examine a sample of brain after death. The following changes are more common in the brain tissue of people with AD: a) "neurofibrillary bundles" (coiled protein fragments that accumulate in the nerve cells) b) "neuritic plaques" (pathological aggregations dead and nekroumenon nerve cells, other brain cells, and protein) c) Senile plaques "(areas where products of nekroumenon nerve cells have accumulated rounds of protein).

When the destruction of nerve cells (neurons), there is a reduction in chemicals that help nerve cells to send messages to one another (called neurotransmitters). As a result, areas of the brain that normally operate together disconnected. The concentration of aluminum, lead, mercury and other substances in the brain is no longer considered a cause of AD.[1]

Symptoms

Dementia symptoms include difficulty in many areas of cognitive function, including: the language, the memory, the perception, the emotional behavior or personality, cognitive skills (such as calculation, abstract thinking, or judgment). Dementia usually manifested initially as memory disorder.[2]

Lifesaving early diagnosis

Early and accurate diagnosis helps the patient and the caregiver to be better equipped to smoothly go through the various stages of the disease. The correct diagnosis is also provided an effective treatment[2]First family members evaluate the problems of their man. If you find suspicious symptoms should contact a doctor who will make the official diagnosis. The caregiver helps the doctor: a) to diagnose the dementia syndrome b) to evaluate the efficacy of drug therapies c) recognise and treat problem behaviors. Doctor helps the caregiver: a) to accept the role without anger and guilt b) to confront the patient with a realistic and effective c) to handle the symptoms of the disease

A seven older adults 84 (5) years with disturbance of equilibrium and (Berg Balance Scale [BBS] score <52 units. Making use of the wii games safely about 50 sessions with duration of 31 minutes. Improved the balance in the scale Berg Balance Scale [BBS] score 53 points.[3]Increase their attention, improve mood and relieve stress.[4]

Interactive games

Interactive games are characterized toys which help the people to move because they combine exercise with visual commands (image) helping people to participate in the game. Interactive games focus on large muscle groups and not improving fine motor. The Wii platform allows the player to fully participate in the movement of the whole body and not just two fingers.[5]

Using interactive games

The interactive games are used by: physiotherapy, occupational therapy, psychotherapy [5]
To arrive at a physiotherapy session interactive games the equipment required i*s:* a TV or computer or table, camera on the screen to understand the movements of the patient, and an interactive arm mounted at the upper end, which functions as a remote control.The elderly perform various exercises in virtual environment

Advantages interactive therapy

Using interactive games bring the following: Improved the aerobic exercise. Improve the balance. Improve the flexibility. Improving these bodily functions help improve the physical condition of the patient.

Results

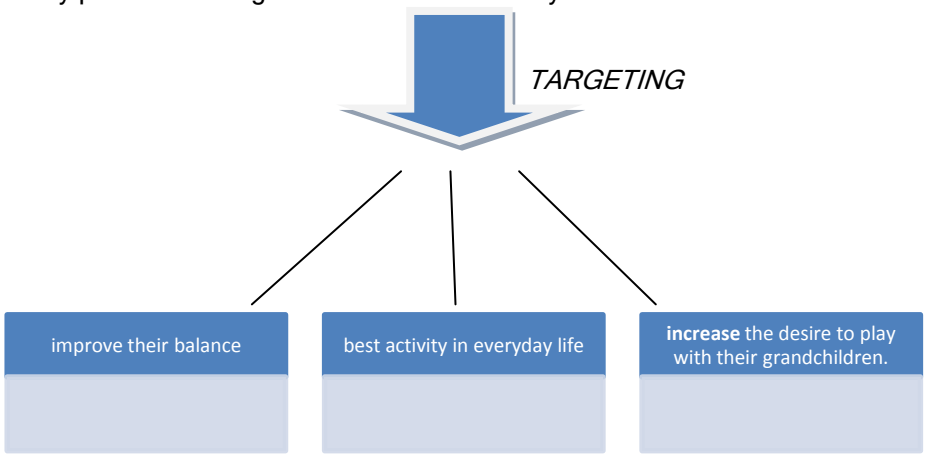
In patients with dementia helps: a) To increase their attention b) To improve their disposal c) To relieve stress. In patients with dementia increase physical activity and concentration[4,6]Further helps reduce orders to execute the people activity and greater independence. Results in healthy elderly subjects are shown in Figure 1.[3]

Conclusions

Interactive games provide positive results in people with mild dementia and healthy elderly subjects because in addition to improving their fitness improves concentration and reduces stress for patients and helps to reduce the orders of repetition frequency for performing the exercise.

The authors declare that they have no conflicts of interest.

Figure 1. Healthy elderly persons making use of the interactive toy aimed at



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Metabolomic analysis in brain research

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Keywords: Metabolomics -Systems biology and medicine -Brain complexity -Neurodegenerative diseases - Metabolic network analysis

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Abstract

Background: Metabolic phenotyping corresponds to the high-throughput quantitative analysis of the concentration of the small molecules that act as reactants or products in the metabolic reactions and play a regulatory role for the activity of many proteins (metabolome). The metabolic profile provides a wide perspective of the metabolic physiology of biological systems, analyzing simultaneously tens to hundreds of molecules of physiological and pharmacological interest. Especially for central nervous system (CNS), given the high degree of complexity of mammalian brain, the holistic analysis of its molecular physiology at different levels of cellular function can further our understanding of the molecular mechanisms underlying neurological disorders. Even though it is the newest "omic" analysis platform, metabolomics has been applied in the investigation of various neurodegenerative disorders including dementia. For its application in clinical practice it is still at its standardization phase, most of the results are relied on the use of animal models. **Objective:** In this review, we support the value of metabolomic analysis and illustrate the new directions and opportunities that it can lay for the investigation of neurodegenerative diseases. We also demonstrate the challenges of designing and setting up a reliable metabolomic study in brain research, which, among other technical parameters, has indeed to take into consideration the sex differentiation and the complexity of the brain physiology manifested in its regional variation. **Conclusions**: The vast utilization of metabolomics as a major systems neurophysiology tool requires the standardization of experimental design, pre-analytical, analytical and data analysis steps.

Introduction

The systems biology revolution and its effect on brain research

Since the 1960s, the central dogma of biology supported in general a unidirectional flow of information from gene to transcript to protein, while enzymes catalyze metabolic reactions and lead to changes in the phenotype. This "linear" thinking for the relationship of genotype with the phenotype that has pertained molecular biology research could not reveal complex interconnections between molecules that generate systems properties or behaviors which are fundamental to life [1]. The ability for the parallel quantification of tens to hundreds to thousands of molecules that was offered from the new technologies for high-throughput biomolecular analysis (known as omic technologies) allowed for a more global perspective of the biological systems to be obtained at the molecular level rendering obsolete the "conventional" reductionist approach [2]. The consideration of "one gene/one enzyme/one function" has collapsed, while the genotype-phenotype relationships arise from a much higher underlying complexity [3]. Network biology and medicine deal with this complexity reconstructing maps of biomolecular interactions at different molecular levels of cellular function and between them, using systematic and standardized approaches. Elucidating the structure and regulation of these biomolecular networks can lead to a comprehensive understanding of the molecular physiology, and under disease circumstances the pathophysiology of biological systems.

The revolution of the holistic quantitative analysis of the molecular physiology that characterizes our post-genomic, systems biology era, allowed neuroscientists to move from the study of individual molecules or circuits to a systems-level perspective of the complexity of brain function. This systemic approach is mandatory for the study of the brain, as it permits us to view specific molecules of each level of neuronal function (genes, transcripts, proteins and metabolites) in the context of all others [4]. Thus, we can reveal molecular interrelationships that underlie systemic properties of brain function [4-6]. The mammalian brain contains 10^8-10^{11} neurons and a greater number of glial cells that are not homogeneous but consist of subpopulations of different anatomical, genetic and physiological properties. This high complexity of brain tissue stands for its characterization as a temporally and spatially multi-scale structure [7]. Defining the various cell types and their functions in different brain regions is essential for the understanding of the neural circuits. Neuroscientists examine the structure, the organization and the interconnected functions of brain that together form the biological basis of cognition. Although recent applications of neuroimaging techniques have provided unique insights into the brain structure and function, the majority of studies represent the brain as a static system without explaining the underlying emerging dynamic phenomena. To obtain a comprehensive perspective of the brain architecture and function it is necessary to analyze this tissue as a dynamic network of biomolecular interactions divided into subdomains or regions the properties of which are not linearly dependent, and cannot be understood using fundamental reductionism. Thus, the high-throughput quantitative nature of omics research distinguished the hypothesis-driven studies performed in the majority of neurobiology laboratories from the discovery-based which generate novel hypotheses and new directions of research. The discovery-based studies may lead to the development of sensitive and accurate diagnostic tools, based on multi-molecular biomarker profiles, and provide clues for new therapeutic treatments and drugs. The systems biology research is powered by the collaboration of expertise of several, traditionally distant,

scientific fields, involving biology, chemistry, physics, computer science, engineering, statistics and applied mathematics [2,4,8].

The emerging role of metabolomics in the study of CNS disorders: new directions and opportunities

Metabolomics is the most recently introduced, but currently the fastest growing, "omic" analysis platform that refers to the high-throughput analysis of the metabolic network state of a biological system through the simultaneous quantification of the concentrations of all (measurable) free metabolites of low molecular weight, i.e. the metabolic profile, under various physiological conditions. Since the concentration of the free small molecules affect and are affected by the metabolic reaction rates (or fluxes), the metabolic profile provides a metabolic fingerprint of a particular biological system, equivalent at the metabolic level to the transcriptional and protein profiles, analyzed through transcriptomics and proteomics, respectively. The metabolic profile provides us information about the *in vivo* enzymatic activity, which cannot be provided by the profiling of the other molecular levels of cellular function. Comparing the metabolic profile of a system at various physiological states can further our understanding about the regulatory mechanisms governing the metabolic network activity. Since the metabolic network activity is regulated by post-transcriptional and post-translational events, but also affects them while also reflecting changes in the extracellular environment, metabolomics is a crucial tool for deciphering the relationship between genotype and phenotype, and investigating the effect of modifications in the cellular environment [4,9,10]. Significant advantages of metabolomics is that it can be applied to biological systems even when they are under transient physiological conditions and its application does not require extensive knowledge of the metabolic network structure [10]. Rather, metabolomics data can help in the reconstruction of the active metabolic network. This is important in the context of brain research, since there are still a lot of open questions regarding the mammalian brain metabolic network and its subregional differences. Considering the role of metabolism in the context of the overall cellular function, metabolomic analysis is an integral part of systems biology research. Especially in brain research, it can prove substantially elucidative as it has been indicated by reported studies, contributing to the creation of a map of the human neural network, known as connectome, that can further our understanding of the complex brain functions [11].

Many neuropsychiatric and neurodegenerative diseases have been associated with long lasting abnormalities in metabolic pathways. Notably, there is increasing evidence linking mitochondrial dysfunctions with CNS diseases. Moreover, impairments in the antioxidant system, signaling pathways, membrane composition, immune response and neurotransmission have been identified among other metabolic changes [6]. Until recently, neuroscientists have focused on investigating few selected metabolites at a time changes in the concentration of which have been considered as credible markers of the investigated pathophysiology. More often, these metabolites are epinephrine, norepinephrine, acetylcholine, dopamine, serotonin, glutamate/glutamine and γ-aminobutyric acid (GABA), molecules that act as neurotransmitters, thus changes in their concentration have been mainly studied in the context of this function. However, these metabolites are also intermediates of a larger metabolic network, which, if studied with a more global perspective, can provide significant clues about the underlying mechanisms of serious mental illnesses and neurodegenerative diseases, helping also in designing more effective therapeutic treatments and drugs [6,11]. Although some progress has been made in the treatment of CNS disorders a significant proportion of patients do not respond to the currently used therapies or suffer from side effects [12,13]. Inheritance is an important factor that affects the field of pharmacology and led to the development of pharmacogenetics and then pharmacogenomics research. However, many other factors like age, gender, environment, disease stage or subtype contribute to drug response variation. The new branch of pharmacometabolomics is defined as the determination of the outcome of a drug in an individual based on metabolite signatures [13,14]. It provides tools for mapping the various metabolic effects of drugs and identifying pathways that contribute to drug-response phenotypes. Moreover, another highly important contribution of pharmacometabolomics is the sub-classification of patients in terms of treatment efficacy, safety and pharmacokinetics in clinical and preclinical settings. Pharmacometabolomics in conjunction with pharmacogenomics are very promising for improving personalized healthcare and contribute to the selection of the optimal treatments for specific groups of patients [13,14]. To achieve the global perspective of brain function, we should also carefully study the differences in the metabolic network activity and regulation of the various regions of the brain that have been evidenced to have different roles and biochemical characteristics.

As the human life expectancy expands, research about neurodegenerative diseases related to aging, like Alzheimer's disease (AD) has substantially increased in the recent years. There is need for enhancing our knowledge about the disease progress and identifying possible biomarkers for early diagnosis. The most frequently used diagnostic means for AD are currently imaging techniques, including positron emission tomography (PET) and single photon emission computed tomography (SPECT) that usually investigate changes in the blood flow, oxygen and glucose metabolism in the brain of AD patients [15]. However, the focused character of these techniques to a small part of metabolism in combination with the related cost and the exposure of patients to radioactive probes makes untargeted metabolomic analysis of biological fluids, as blood and cerebrospinal fluid (CSF), a very attractive option [16]. Fewer studies have applied metabolomics to post-mortem tissues of human brain [17,18]. With respect to the usage of animal models, metabolomic studies have been conducted to transgenic animal models of the disease [19]. The results of such studies using various analytical techniques have demonstrated mitochondrial alterations, generation and accumulation of ROS, inflammatory responses, signal transduction defects, neurotrophic support failure synapse loss, and cytoskeletal impairments. Focusing on metabolic intermediates, the aforementioned alterations concern changes in the amino acid and lipid metabolism, mainly the biosynthesis of ceramides and sphigomyelins, urea cycle intermediates, neurotransmitters and molecules with antioxidant properties [17,18]. Still, more advanced and extensive studies are required combining transcriptomic, proteomic and metabolomic analysis to better understand the molecular basis of AD. Metabolomics can indeed be a powerful tool in brain research. It is also noted that metabolomics does not require special technology, thus it can be carried out at a small fraction of cost than transcriptomics and proteomics. For the

quantification of the concentration of small molecules, classical analytical chemistry equipment is used: Nuclear Magnetic Resonance (NMR) spectroscopy and/or mass spectrometry (MS) integrated with gas or liquid chromatography (GC or LC) [9,10]. Thus, establishing metabolomics facilities for large-scale use can be less costly and requiring less time for personnel training than transcriptomics and proteomics. Finally, metabolism being well conserved among biological species, there is no need for the development of different probe sets, acquisition methods or database structures for each biological system under investigation [10]. However, the broad deployment of the metabolomic analytical platform to systems medicine in general and brain research in particular requires its standardization for accurate, reproducible and validated performance. Many issues from the experimental design to the sample collection and handling, the selection of the analytical technique for the profile acquisition up to the data normalization and filtering methods and the metabolic network reconstruction and analysis should be carefully considered for a successful application of metabolomics and the extraction of accurate biologically-relevant conclusions, as discussed in the following sections.

Metabolomics in systems biology: a multi-step high-throughput biomolecular analysis

Metabolomic analysis in systems biology is a multi-step procedure comprising of both experimental and computational parts as shown in Figure 1. The experimental section involves the pre-analytical steps of (a) the experimental design and study group selection and (b) the sampling procedure, including any required sample handling, up to the quenching of all enzymatic processes and any necessary storage and transport methods to the metabolic profile acquisition laboratory. The standardization of the pre-analytical steps is very important for a successful metabolomic analysis, which will provide biologically relevant conclusions, free of any experimental biases. The analytical part includes (a) the extraction/isolation of the free metabolites from the biological system, (b) the derivatization of the free metabolite extract to metabolite derivatives of specific properties to be measured with the selected analytical technique, if required and (c) the metabolic profile acquisition using mainly NMR spectroscopy and/or MS integrated with GC or LC. Derivatization is imperative in the case of GC-MS metabolomics, because most metabolites are not volatile. Through their reaction with a derivatization agent, they are transformed to volatile and thermally stable derivatives. The selection of the analytical technique is based on criteria of availability, sensitivity, accuracy, need for metabolite identification and need for high-throughput or targeted analysis of specific compounds. In this context, mass spectrometry is preferred for untargeted high-throughput analysis, but with a substantial number of unknown compounds, while NMR spectroscopy provides information for the identification of the measured metabolites and higher quantification accuracy, but has lower throughput and sensitivity than mass spectrometry [10,20]. Moreover, GC-MS has been preferred over LC-MS for the study of the non-polar metabolite profile in the context of central carbon metabolism, because the separation of the molecules in the chromatographic column is higher in the gas compared to the liquid phase, while the available libraries of GC-MS profiles of compounds of physiological and pharmacological interest are more extensive than the corresponding for LC-MS [10,20]. However, GC-MS can only detect compounds up to a particular molecular weight (formerly 650 atomic units, in more recent equipment this has been increased to 1000 atomic units). If possible, integration of analytical techniques could provide more elaborate results, as each platform provides complementary information to the others [21]. A more recent approach considering time as a significant parameter of the high throughput nature of omic technologies refers to the omission of the chromatography part of analytical platforms. Although faster chromatography is possible using shorter columns and higher linear velocities, it suffers from coelution, matrix effects and decreased sensitivity. On the other hand, chromatography-free systems provide the opportunity of injecting thousands of samples per day through direct infusion of flow injection to mass spectrometers [22]. However this type is not a precise way to conduct metabolomic analysis, it is usually applied for discriminatory (and not peak identification) purposes.

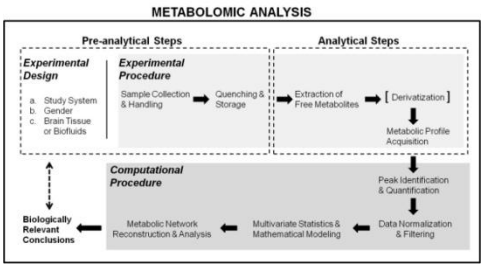

Figure 1. Metabolomic analysis is a multi-step procedure involving both experimental and computational sections.

The computational part of the metabolomic analysis starts with the peak identification and quantification, which depends on the analytical platform that is used for the profile acquisition. The standardization of this part of the analysis and the formation of rules for the submission of the metabolomic data to public databases for combined analysis and meta-analysis between laboratories is a very hot subject of research and collaborative effort among the metabolomic laboratories [23] Commercial peak libraries (e.g. NIST GC-MS peak library), publicly available libraries populated from national or international consortia (e.g. Human Metabolome) [24] and/or in-house libraries of standard compounds are used for the peak identification. Algorithms and relevant software for peak area quantification in an automated way have been developed [25]. In a fully high-throughput automated way, some researchers choose to consider all measured features in the following multivariate statistical analysis for the extraction of biologically relevant conclusions. In the case of NMR spectroscopy, the landscape of the acquired spectrum and the relative quantity of the various peaks provided information about the chemical structure and the isotopic labeling of the measured compounds. In the case of mass spectrometry, a “metabolite-centric” approach, in which one marker ion is selected for each metabolite derivative and the quantification of its peak area is used as representative of the concentration of the particular metabolite derivative has also been used [10,26]. While more time-consuming than the approach that uses all the quantified features in the multivariate statistical analysis, the “metabolite-centric” quantification approach is more selective, avoiding the

introduction of mathematical artifacts from the consideration of non-independent features in the statistical analysis [10]. Figure 2 shows an example of the "metabolite-centric" quantification of N-acetylaspartate in the GC-MS metabolic profile of a Balb/cJ male mouse cortex measured in our laboratory. In Figure 2A, one may see the MS-reconstructed gas chromatogram of the trimethylsilyl (TMS) derivatives of the free polar metabolite extract of the cerebral cortex sample (for full protocol see [27]. Based on the NIST peak library (version 2.0) and our in-house standard compound peak database, the peak of the N-acetylaspartate derivative is identified at 24.170 min retention time with the mass spectrum shown in Figure 2C, involving the fragment ions with molecular weights 274 (at the highest concentration), 184, 230 and 245. It is noted that in GC-MS, the molecules after coming out of the chromatographic column are ionized through high energy electron bombardment and get fragmented. The ion fragmentation pattern (shown in the mass spectrum) along with the retention time of the metabolite derivative in the chromatographic column (shown in the MS-reconstructed chromatogram), help in the peak identification. Being the most discriminatory and with the highest signal to noise ratio among all the fragment peaks that correspond to the N-acetylaspartate derivative, the fragment ion with molecular weight 274 is selected as the marker ion for this derivative and its peak area as representative of the concentration of N-acetylaspartate in the cortex metabolite extract (Figure 2B). In the "feature-centric" approach all fragment ions may be considered in the analysis.

A major step in the computational part of metabolomic analysis is the normalization and filtering procedure [10,20,28]. Experimental biases are introduced at each of the experimental steps at the pre-analytical and the analytical section. Normalization algorithms are applied to correct the omic data for these experimental biases so that the remaining differences among the normalized metabolic profiles are due only to biological reasons [10,29]. Quality control and data validation criteria are also applied to filter out low reliability measurements, outliers and technical artifacts from the final normalized dataset. The latter is used for data mining and multivariate statistical analysis to extract biologically relevant conclusions. We use clustering algorithms to identify subsets of samples/physiological states or metabolites that have similar profiles based on a particular similarity measure, which in mathematics is named in the opposite way as "distance metric". Among the clustering algorithms, the most frequently used is the hierarchical clustering method (HCL) [30]. A second issue that is encountered in the analysis of the high-dimensional omic profiles is the visualization of their relative differences in the 3D space. To address this problem, we use profile transformation algorithms that appropriately project the variation in the original data to be (potentially) visualized to its large extent within the 3D space. The most reknown of this type of algorithms are principal component analysis (or PCA) [31] and partial least squares regression analysis (PLS) [32]. Finally, we often need significance analysis algorithms to examine whether two sets of samples/physiological states can be statistically discriminated based on their metabolic profiles. Moreover, we want to identify the difference in the concentration of which metabolites is characteristic of this discrimination. The Student's t-test and ANOVA algorithms are used in the analysis of omic profiles, however, they both require that the data can be considered to follow a particular distribution. In the case of the metabolic profiles, this is not true, as the metabolomic data are correlated according to the structure and regulation of the metabolic network. This is the case for all omic profiles, which are bound based on the corresponding biomolecular network. For this reason, a multivariate significance analysis, called "significance analysis for microarrays (SAM)" [29] was initially introduced for the analysis of the transcriptomic profiles produced from the DNA microarray analyses, but which can be similarly applied to any set of omic data (e.g. [27,33]).

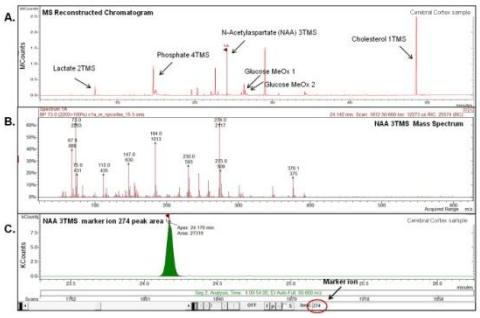

Figure 2. Metabolite derivative peak identification in GC-MS metabolomics and area quantification based on a selected markerion. The example shows A. the MS-reconstructed gas chromatogram of the TMS-derivatives of the polar metabolite extract of a cerebral cortex tissue sample isolated from a male Balb/c mouse (see full protocol in [27]); the peaks of the glucose two derivatives and of the single lactate, phosphate, N-acetylaspartate (NAA) and cholesterol derivative are indicatively marked; B. the mass spectrum of the NAA derivative, which the characteristic ion fragmentation pattern; the fragment ion with molecular weight 274 is of the highest relative quantity; C. the quantification of the NAA derivative based on the peak are of the fragment ion with molecular weight 274, which has been selected as the marker ion of this metabolite derivative.

In biomolecular profiling analyses, there are usually two main objectives: the first refers to our ability to discriminate between two groups of samples based on the acquired biomolecular profile(s), identifying thus characteristic multi-compound concentration profiles that can serve as biomarkers for early and accurate diagnosis of a particular change in the physiology of the investigated biological system. The second objective concerns our ability to further our understanding of the molecular processes underlying a particular pathophysiology based on the acquired concentration profiles. In the case of the metabolic profiling analysis, the latter can be accomplished if we analyze the results of our analysis in the context of the known metabolic network structure and regulation of the biological system under investigation. In the post-genomic era, the availability of the genomic information contributes to the metabolic network reconstruction of a particular biological system. For this purpose, we use data from major metabolic databases, like KEGG (http://www.genome.jp/kegg/; [34]), Metacyc (http://metacyc.org/; [35]) and Expasy (http://www.expasy.org; [36]). Moreover, we mine information from the literature about the detected activity of certain enzymes and compartmentalization issues. Final, our own metabolomic data can be also used to indicate the activity of certain pathways in the biological system of interest.

Issues to be considered in brain metabolomics

Taking into consideration that metabolism is the most dynamic molecular level of cellular function, and very sensitive to changes in the cellular environment, a systemic and systematic study of the mammalian brain metabolic physiology under healthy and pathophysiological conditions requires careful design and execution of both of pre-analytical and analytical steps (see Figure 1). Issues related to metabolomics analysis in general and brain metabolomics in particular, are discussed below in the context of the various phases of the multi-step profiling procedure that is shown in Figure 1.

Pre-analytical steps

Experimental design

There are three main biological parameters that scientists need to take into consideration when designing a metabolomic analysis study in brain research: (A) whether the study will involve tissue or biofluid analysis, (B) the study system and (C) the gender (Figure 3). (A) and (B) are strongly related, especially when human studies are concerned.

A. Selection of brain tissue or biofluids

A serious problem in neurophysiology studies in humans is the inability to directly analyze the brain tissue. Most findings rely on analyses of biofluids, mainly the blood plasma or serum and CSF. Blood (plasma and serum) can be easily accessed. It is believed that the neural impairments associated with neurodegenerative disorders, like Alzheimer's disease, may have any impact on peripheral tissues including the blood composition [16]. However, blood being a mirror of the physiology of all tissues, there is a doubt as to whether sensitive and accurate biomarkers of a neurodegenerative disorder should be sought in the blood composition. Especially, given the blood-brain barrier that limits the passage of metabolites form the periphery to the brain, there is a disagreement about the extent of the correlation between changes in the peripheral tissues compared to those in CNS [16]. In addition, there is still limited information about the relation of the blood composition with the metabolic physiology of peripheral tissues, in the context of an inter-organ metabolic network reconstruction [37]. On the other hand, CSF has been extensively used in brain research, because its composition is considered to be better reflecting the physiological state of the brain compared to blood [38]. However, there are serious limitations in its use in brain studies concerning mainly the sample collection procedure, which is highly invasive and cannot be easily collected from healthy individuals, as described in the sample collection and handling section below. Thus, in most cases, the control group of the study comprises patients of other than the investigated CNS disorder, from whom CSF has been collected for the analysis of their disease. This contributes to lack of reference CSF metabolic profiles and high variation between the results of various studies. It is also requires sophisticated experimental design and statistical methods for data validation in order for the results to really reflect the changes due to the investigated CNS disorder.

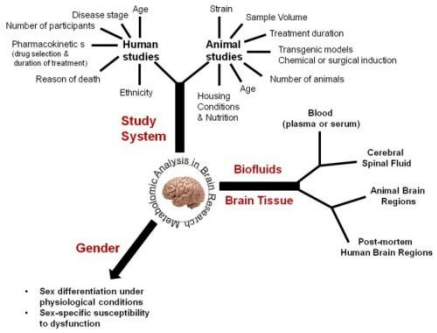

Figure 3. Three main biological parameters that scientists need to take into consideration when designing a metabolomic analysis study in brain research: (A) whether the study will involve tissue or biofluid analysis, (B) the study system and (C) the gender.

Usually, the best way to study the pathophysiology of a disease is to have direct access to the respective tissue. In human brain research, brain banks provide neuroscientists with port-mortem tissues [39]. Studies of post-mortem human brain have been carried out for Alzheimer's disease, schizophrenia and bipolar disorder [39,40]. These tissues are quite valuable in enhancing our understanding of the molecular mechanisms of neurodegenerative and psychiatric diseases. Obviously, they are in limited availability, and varying with respect to the patient's age, gender, disease state, type and duration of pharmaceutical treatment, reason and way of death, time after death at which the tissue was isolated, type and duration of storage [39]. Due to these limitations in using human brain tissue in biomedical research, scientists have substantially relied on the use of animal models in brain research, mainly rodents, rats and mice. Although animal models provide important benefits in brain research, there are not animal models for most of the neurodegenerative and psychiatric diseases, the study results of which could be easily extrapolated to human. Especially in the aging related neurodegenerative diseases, most animal models are transgenic and can be used to monitor the progression of the disease, however, they cannot provide information about the cause of these multifactorial diseases.

When brain tissue studies are designed, one has to consider the confirmed regional variation in the molecular physiology of the brain. Mammalian brain is a multi-scale structure comprising various brain regions with different physiological and biochemical roles. In most studies, the researchers usually choose to study one brain region that has been associated with the onset and/or the progression of the investigated disease. However, the integrated view of the changes that a particular pathophysiology exerts on the metabolic activity of the various brain regions may prove quite valuable in understanding the disease [19,41,42].

B. Study System

The selection of the patient and control groups with respect to the medical history, disease state, age, lifestyle in the case of human studies and of the disease model in the case of animal studies is very crucial for the success of any

neurophysiology analysis. It becomes even more significant in the case of metabolomic analysis, because of the high sensitivity of the metabolic profiles to any implicated variations originated from a nonsystematic selection of the sample groups. Especially when drugs are used as most are small molecules that can interfere with the measurements of the intracellular metabolites, the type of drugs, the dose and the duration of the treatment should be considered for better correcting, filtering and interpreting the acquired metabolomic dataset.

In the case of the animal studies, the standardization of animal nutrition, housing and handling conditions becomes of great importance. Housing and handling conditions should be strictly controlled to avoid inducing stress and aggressive behavior to the animals, which could affect their metabolic physiology and thus have consequences in the study results. Another significant parameter that may affect the metabolic physiology of the animals is the selection of the food, the composition of which has to be standardized and tailored to the objective of each study.

Furthermore, animal disease models might be transgenic or based on the chemical or surgical induction of the disease. Each study system has advantages and limitations that have to be considered by the scientist in the context of the examined disease and the goal of the investigation. In both cases, the selection of the animal strain is usually an important parameter to be considered as it might affect the acquired results. In the case of chemically or surgically induced disease models, the animal age at which the surgery occurs or the chemical induction starts and the duration of the treatment should also be carefully considered.

In both human and animal studies, the number of samples in both the control and the disease groups is of great importance. A large number of animals increase the confidence in the acquired results as it decreases the impact of biological variation between the animals. On the other hand, there are ethical issues concerning the number of animals used for scientific purposes, creating limitations according to the respective guidelines. In both animal and human studies, the size of the available sample is a fundamental factor for the design of the metabolomic analysis. If the size of a particular brain region from an animal model or the volume of the available biofluid samples is at the detection limit of the analytical technique used for the metabolic profiling, pooling of brain regions or biofluid samples from different animals may be necessary to obtain credible results. However, the pooling hinders the individualized study of each animal or patient separately.

C. Gender

Many studies have revealed that sexual differentiation in the mammalian brain physiology is a highly regulated phenomenon throughout life that involves genetic, epigenetic, molecular and cellular mechanisms [43]. As the effect of a particular pathophysiology and the impact of a therapeutic treatment may greatly differ between sexes, the final conclusions of a study in one sex cannot be considered as directly applicable to the other [44]. It is thus imperative that the experimental design includes analyses of samples from both sexes, given that neurological and neurodegenerative symptoms are manifested in a sex-dependent manner.

Sample Collection and Handling

The appropriate sample collection and handling is a key step in a metabolomic analysis to avoid metabolite loss and/or significant alterations in the metabolite concentrations during the collection and handling procedure before the enzymatic quenching. International directives for sample collection, handling, storage and transport are currently been under development based on data generated from metabolomic analysis of samples collected, handled and stored based on various protocols, In blood sampling, the anticoagulant should be such that it does not interfere with the other molecules in the blood and does not cause perturbations to the acquired metabolic profile. In addition, the blood should be set in ice immediately after collection and the plasma isolation should be carried out as fast as possible. The samples should be directly frozen in liquid nitrogen and stored at -80^{0}C until further analysis. They can be transferred in dry ice. Regarding CSF, its collection requires highly trained clinicians and the procedure is risky and painful for patients and volunteers. After isolation, the samples should be frozen similarly to the plasma samples discussed above. In the case of post-mortem tissue collection, the time after death, the duration and the way of tissue removal, the way of freezing the sample and the duration of storage are key factors for a future well-designed metabolomic study [45].

In the case of animal models, there two crucial parameters that need to be considered when metabolomic analysis studies are designed: (i) the need for perfusion of the animal tissues including the brain and (ii) the way of animal sacrifice and the selection of the anesthetic and the duration of the anesthesia directly associated with the perfusion procedure. When collecting an animal tissue its interaction with the vascular system has to be taken into consideration. Due to this interaction, overlaps between brain and blood metabolites may result in mistaken interpretations [46]. Perfusion protocols for removing blood from the examined tissues should be applied in metabolomic studies, selecting carefully the perfusion agent, usually isotonic saline (0.9% w/v NaCl), and the duration of the perfusion, which should be as fast as practically possible. About anesthesia, it has been shown to potentially cause substantial changes in the metabolic physiology of the animals and thus the acquired metabolic profile [47]. The anesthetic should be selected appropriately and based on the available regulations. It needs to be underlined that the use of dry ice to anesthetize the animals is not appropriate for metabolomics studies as CO_2 may perturb the metabolism of the animals. However, there have not yet been any systematic studies of the effect of the duration of the perfusion in combination with anesthesia in the metabolic profile of the animals.

Quenching and Storage

In all omic studies, especially in the case of metabolomics, it is of high importance that the enzymatic activities in the biological system are stopped as quickly as possible after the collection of the samples. In the case of tissue, a fast cleaning in isotonic saline or PBS is required before quenching. The latter is usually performed with the use of liquid nitrogen. The samples should be stored at -80^{0}C and transferred to other laboratories in dry ice. However, there are serious indications that extended storage may cause alterations in the samples that could affect their quality for analyses.

Systematic studies of these changes in the metabolic profile of the stored samples are currently under way in many metabolomic laboratories. The results of these studies are significance for the design and handling of biobanks.

Analytical steps

Extraction of free metabolites

There is no extraction method for the entire metabolome. The most often employed protocol used methanol and water for the extraction of the polar metabolites, e.g sugars, sugar acids, organic acids, sugar phosphates, amino acids and some low molecular weight lipids. For lipidomic analyses, chloroform should be used as the extraction agent [10]. There are various extraction protocols, some specialized to certain chemical compounds and could be selected appropriately according to the objective of each study.

Computational Procedure

Details about the analytical procedure, the peak identification and quantification, the normalization and filtering process and the data mining and multivariate statistical methods are provided in the previous section. The issues are common for any system and not only associated with brain research. However a major issue that needs to be addressed in the context of the analysis of the brain physiology is the accurate reconstruction of the brain metabolic network, so that any metabolomic analysis results could be interpreted in its context.

Metabolic Network Reconstruction

Most metabolomic analyses of brain tissues provide a list of the metabolites the concentration of which is detected as significantly different between two sets of samples. However, the list alone cannot provide a more global view of the changes in the metabolic network activity from one set of samples to the other. The reconstruction of the brain metabolic network is necessary based on available information from the metabolic databases, the literature and available metabolomic data, so that the significantly differentiated metabolites can be visualized in the context of the metabolic reactions and metabolite interrelations. In [27], we reconstructed the mouse brain metabolic network based on metabolic databases, neurochemistry textbooks and more than 80 papers each referring to individual reactions or specific pathways (Figure 4). As the brain metabolic physiology has been conventionally studied in a fragmented way, focusing on specific pathways and/or brain regions, there are still many open questions regarding the potential activity of certain enzymes in the brain, the reversibility of particular reactions and the ability of the brain to synthesize under particular circumstances certain metabolites that are provided through the blood brain barrier. Extensive analysis of the brain metabolic physiology in animal models using also isotopic labeling methods must be carried out to fully and accurately answer these questions. When reconstructed, the metabolic network could be appropriately colored to indicate the metabolites the concentration of which was significantly higher (red) or lower (green), in a group of samples compared to another. In this way, conclusions about the up- or down- regulation of specific metabolic pathways in one set with respect the other can be made and metabolic alterations associated with the difference between the two sets of samples can be revealed (see example in Figure 4).

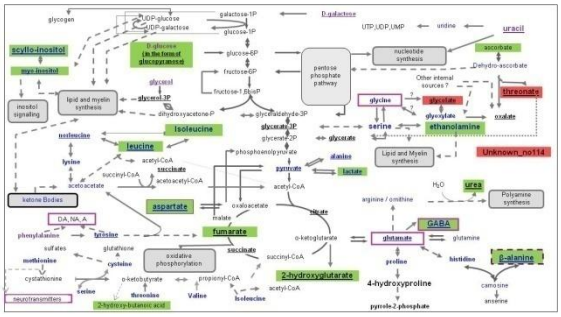

Figure 4. The reconstructed metabolic network of mouse brain in [27], in which metabolites have been indicatively color-coded as red and green, respectively, to indicate their significantly higher or lower concentration in a set of samples compared to another.

In the case of biofluid metabolomic analysis, the interpretation of the results in the context of the brain and peripheral tissue physiology is more challenging. There is a need of an inter-organ metabolic network connecting the concentration of a metabolite in a biofluid with its concentration in respective tissues. In [37], we reconstructed such an network to connect the blood metabolic profile with the metabolic network of liver, adipose and muscle tissue. To the best of our knowledge, there has not been such model connecting CSF composition with the brain metabolic network, however, the network of Figure 4 could be used in this case, as it includes all metabolites that are provided to the brain through the blood brain barrier.

Conclusions and future directions

In the systems biology era, there is a shift from the reductionist approach supporting a linear unidirectional flow of information from genotype to phenotype towards the use of high-throughput biomolecular analyses and the interpretation of high-dimensional biomolecular profiles in the context of networks of genes and gene products. Metabolomics emerges as the newest omic analysis that provides a fingerprint of the metabolic physiology of a biological system that can complement the transcriptional and the protein profiles, while providing additional information about the *in vivo* enzymatic activity and regulation that cannot be provided from the monitoring of the other two levels of cellular function.

Metabolomics is at its standardization phase, as it has not been extensively, if at all, applied in many biological systems, including brain research. Issues about the experimental design, the pre-analytical and the analytical steps along with the standardization of metabolomic data validation and handling have to be addressed to support its vast utilization as a major systems biology tool.

In brain research, the revolutionary perspective of systems biology triggers the combination between molecular biology and neurophysiology towards a new challenging research field that could be named as molecular systems neurophysiology. The application of metabolomic analysis to the study of CNS physiology and pathophysiology will further our understanding of the CNS metabolic complexity, expected to provide important insight about the onset, progression and treatment of multifactorial neurodegenerative and psychiatric diseases. Currently available metabolomics studies in brain research have shown that metabolic signatures could be potential discriminatory biomarkers for the early and accurate diagnosis of a CNS disorder. Moreover, pharmacometabolomics can be a strong tool of personalized medicine when defining a therapeutic treatment for a particular patient. However, for the successful deployment of metabolomics in brain research, in addition to the common in all systems standardization issues, the researcher has to select carefully the study group, the physiological conditions under investigation, the brain region(s) or the biofluid(s) to be analyzed. All pre-analytical and analytical steps have to be strictly controlled to avoid experimental biases that can skew the biological results. In addition, a multi-organ study in which the changes in the brain physiology are directly compared with changes in peripheral tissues and the blood could provide a better understanding of the systems function at the body level.

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Authors declare that they have no conflicts of interest

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Neuropsychological evidence of cognitive impairment in a patient with early-onset of Parkinson's disease

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Abstract
Parkinson's disease includes secondary non motor symptoms, besides the prevalent manifestations of movement which reflect its multidimensional nature. Cognitive deficits are some of the most important aspects of the disease on both early and late stages. The early manifestations of cognitive impairment, which signify the onset of dementia disorder, define the development of the disease along with the potential occurrence of psychiatric symptoms and the deterioration rate of motor problems. In particular, during the early stages of the disease, the non motor symptoms with prevalence in memory disorders, concentration problems as well as dominant executive functions and visuo-spatial abilities are likely not to be perceived by the patients themselves. In the early stages of the disease, the neuropsychological tests constitutes a necessary condition in order to identify deficits, capabilities as well as the definition of its progressive course. **Objective:** The objective of this study is the presentation of a patient's case with early onset of the disease which presented mnemonic deficits apart from the kinetic events. **Method:** The test was performed by a neuropsychological battery adapted to the requirements of the disease's nature which includes the recently weighted scale in the Greek population PD-CRS. **Results:** The results indicated difficulties compatible with executive and mnemonic dysfunction as well. There was also total early cognitive impairment. **Conclusions:** The findings highlight the need for early examinations for accurate diagnosis and prediction as refers the course of patient's functionality. The ultimate goal is to exploit the results in the areas of prevention and intervention.

Introduction

Parkinson's disease is considered to be the second most known neurodegenerative disorder after Alzheimer's disease by a preponderance of 3: 2, men versus women, according to most researches. Beyond any variability in diagnostic criteria and methodological differences noted in the bibliography, there has been scientifically agreed an epidemiological prevalence of about 1-2% of the adult population over 60-65 years or 0.3% of the general population. [1-2] According to the literature, it is primarily refered as a movement disorder with prominent symptoms of bradykinesia, resting tremor and rigidity. Generally, Parkinson's disease disrupts posture and gait. [2] It is considered a disease of the basal ganglia, and it is attributed to a dopaminergic nigrostriatal dysfunction as dopamine holds the lead role in motor coordination.[3.4] The locomotor coordination requires an intense neuronal interaction in the basal ganglia which are part of the extrapyramidal system. The cerebral cortex coordinates the incoming information to the basal ganglia to modulate motor control. [4] The probability of disease increases with age without precluding the fact that it could happen at younger ages. [3,1]

In addition to the mainly motor symptoms which are clearly apparent, there are several non-motor symptoms which in recent years have been the focus of research interest and are associated with emotional and behavioral changes. [5] Their recognition is not only useful for the purpose of diagnosis but also because they aggravate the patient's quality of life and they also have an impact on everyday life. [2,1,6] The main non-motor symptoms are: neuropsychiatric symptoms (anxiety / depression), sleep disorders, sexual dysfunction, apathy ,cognitive decline, and / or dementia. In 1817 Parkinson James, with his «Essay on the shaking palsy», described the eponymous disease and suggested that the senses and the intellect remain intact. Today, it is known that the effects of the disease on the cognitive function compose the clinical picture. [7] The incidence of dementia in Parkinson's disease occurs in 28% of patients. Despite this, cognitive deterioration may occur in patients without dementia. Some cognitive deficits are identifiable even in the early stages of the disease [3]. A percentage of 24 to 31% of patients with cognitive deficits will eventually develop dementia. [8] Other researchers reported in a transitional stage between normal cognition and dementia which constitutes mild cognitive impairment (MCI). [9]

The Mild Cognitive Impairment may represent an early manifestation of the clinical spectrum of dementia. [10] The majority of patients show slowness of thought (bradyphrenia) and difficulty in finding the appropriate word [2]. This fact does not constitute a dementia syndrome since it does not adversely affect the patient's functionality. Dementia has been associated with cognitive decline which has an impact on a person's everyday life. The dysexecutive syndrome characterizes dementia due to Parkinson's disease. The reduced ability of organization, planning, and action in target-directed behavior are the main implications to dominant cerebral functions, basic attention to a lesser degree while the comlex attention to a greater one. Many researchers' report [2] visuo-spatial deficits which are more serious than the corresponding ones due to Alzheimer's disease, despite the fact that the capacities of visual perception and recognition remain intact. In particular, deficits are mentioned in visual-spatial perception and visuoconstructive ability.

Also, there are mild effects on speech and action. The main feature is the reduced verbal flow which is more severely affected than that of Alzheimer's disease. The mnemonic functions are impaired less. Researchers report deficits in the ability to learn new mnemonic material, though less severe than those corresponding to Alzheimer's disease. The ability to identify is maintained at a greater degree than that of the free withdrawal, thing which indicates the storage of memory material but not its easy retrieval.

Particularly, the neuropsychological assessment showed that mild difficulties in working memory and episodic memory arise, while the semantic memory is impaired the same as in Alzheimer's disease [2]. While the loss of dopaminergic neurons in the substantia nigra has been connected to the motor symptoms of the disease, the pathophysiology of mild cognitive impairment is less well known. [4,11] Cognitive impairment in this disease is likely to be due to lesions of the neuronal circuits linking basal ganglia and cortex including the prefrontal cortex. Specifically, the executive dysfunction and attention impairments are likely to be due to discontinuity of neuronal circuits connecting the caudate nucleus to the prefrontal cortex. [4] The fronto-subcortical lesions correspond to impairment of attention and executive functions.

This impairment progressively evolves in reduced performance in prefrontal tests, in visuospatial abilities, and in memory . Also, 20-25% of patients may experience cortical damage corresponding to naming weakness and reduced performance in mnemonic tests and cognitive deficits due to cortical pathology, i.e language mistakes [8].

Generally, the mild cognitive impairment is connected with both anatomical and functional changes in the brain. Imaging studies indicate reduced gray matter in the left frontal lobe as well as the two temporal lobes in patients with mild cognitive impairment [4]. In contrast, dementia due to Parkinson's disease has been attributed to both cortical and fronto-subcortical dysfunction [8]. Other researchers suggest that the impairment of some specific functions such as the impairment of semantic memory and visuospatial skills, except the respective executive functions, indicate the transformation of mild cognitive impairment to dementia in Parkinson's disease [12]. The relationship between the motor difficulties in Parkinson's Disease and the impairment of cognitive function is controversial. Some studies support the existence of dementia in cases with rapid progression of motor difficulties or during prolonged disease cases, while other studies indicate the co-existence of dementia symptom with rigidity / tremor.

Also, the relationship between incidence and severity of cognitive impairment and the age of disease's onset as well as the form of its progression remain completely unclear [9]. However, the emergence of cognitive deficits even in the early stages of the disease is negotiable. [5,8] In many cases, cognitive deficits can not be observed clinically or by the patients themselves, nor within their environment, while being detectable with neuropsychological tests. [4,13,14] In order to cover the full range of cognitive deficits and to predict the progressive course of the disease, the neuropsychological battery to be administered to patients should include tests that will highlight both the cortical and the subcortical dysfunction. [8] A neuropsychological tool with high validity and reliability, particularly useful for the detection of cognitive deficits is the Cognitive Rating Scale Parkinson's Disease (PD-CRS) recently weighted in the Greek population. [15] ΚΝΕ-ΝΠ is the Greek version of Parkinson's Disease-Cognitive Scale (PD-CRS) [8]. This scale controls both the cortical and subcortical functions. [15] From the above mentioned we conclude that cognitive impairment in Parkinson's disease shows an heterogeneous condition with a range of pathological changes which reflect its multisystem nature [7,8] The cognitive deterioration and possible transformation into dementia are causing concern among the patients' caregivers as refers care anticipation.[3]

The objective of this study is to evaluate the patient's cognitive function in the early stages of the disease and to study the findings resulting from the administration of a full neuropsychological battery comprising the main knowledge areas which are impaired in early stages of Parkinson's disease. This case is interesting because it studies a patient with early onset of Parkinson's disease with motor symptoms who receives no medication. The evaluation findings are of great interest in determining the diagnosis, prediction of the progressive course of the disease and the therapeutic neuroprotective strategies. [10]

Material and Method

Participants

The S.K is a patient, aged 51, who observed the first motor symptoms (tremor at (L) top limb) one (1) year ago, while the last three months he reported that they have extended to the (L) bottom limb. He takes medication and went for evaluation of cognitive functions because of reported memory weakness.

Material

A neuropsychological battery was administered to evaluate the cognitive areas likely to show deterioration due to Parkinson's Disease: The MMSE [16], the Trail Making Test (A & B) [17], the Stroop Neuropsychological Screening Test (SNST) [18] and the PD-CRS [15]

The MMSE quickly assesses the general cognitive state of a person. [16] The TMT evaluates the perceptual speed, visual-motor tracking, shared attention and mental flexibility. [18] It is used in two conditions: The condition A where the interviewee is asked to join the numbers from 1 to 25 in a continuous line whlile the execution time is being recorded. In condition B, the subject is asked to join and match letters and numbers alternatively from 1 to 13 whlile the execution time is being recorded again. The SNTS evaluates adjustment speed,

selective attention, and mental flexibility. [18] It is used in two conditions: During the first, the interviewee reads words that are printed in different colors and the reading time is recorded. In the second condition the examinee is requested not read the words but mention the color of each word. PD-CRS includes cortical tests such as: Juxtaposition / Naming of images, copy a clock and subcortical tests such as: the direct recovery of verbal memory, maintain attention, working memory, the spontaneous clock drawing test , the recall of verbal memory, verbal flow switch , verbal flow actions.

In juxtaposition / naming participants were asked to name objects presented schematically or parts of objects. (e.g hook). In clock copy, the interviewee is asked to copy a designed clock. In the immediate recall of verbal memory, a word list is visually given to the examined who is requested to read aloud and immediately withdraw them. The process is repeated three times so that the examinee to be able to recall as many words as possible. The examinee recalls the same word list after about half an hour. In attention maintaining subtest the examinee is verbally given 5 couples series of words and numbers with increasing elements per couple and is requested to report immediately after hearing the number of letters they hear. In working memory subtest the interviewee hears five pairs of words and numbers in random order, but each time increased by one item, and is immediately asked to recall first the numbers and then the letters of the series. In spontaneous clock drawing test the participants were asked to design the face of a clock, to place clock hands at a specific time.

In verbal flow switching, specified time is given to the examinee (1min) and is requested to alternately pronounce (tell) one word from a given letter (K) and a kind of garment. Some instructions / restrictions are given so as to avoid e.g. proper names and word derivatives. During the verbal flow actions the examinee is asked to name human activities in verbal form within a given time.

Methodology

The test was performed after the patient was informed about the purpose of the evaluation, appropriate instructions were given and it lasted approximately one hour. The test was made by a trained clinical neuropsychologist.

Figure 1. Patient's performance in attention tests.

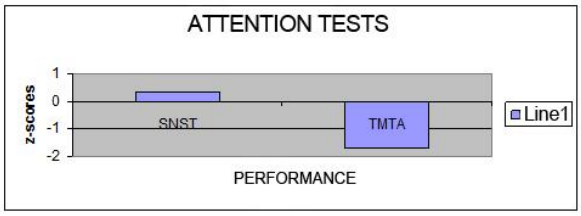
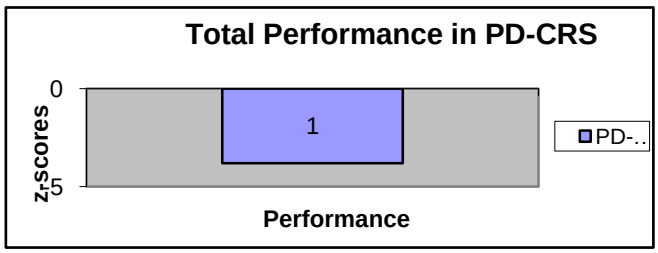


Table 1. Score in subtests of PD-CRS

	Subtest Scale PD-CRS Groups	Score	Maximum performance
Subcortex tests	Immediate recall of verbal memory	5	12
	Attention maintenance	10	10
	Working memory	8	10
	Spontaneous clock-drawing test	9	10
	Delayed recall of verbal memory	4	12
	Verbal flow switch	0	20
	Verbal fluency test	6	30
Total of subcortex score		42	104
Cortex Tests	Juxtaposition / naming	14	20
	Clock copy	10	10
Total of subcortex score		24	30
Total score		66	134

Figure 2. Total performance in PD-CRS scale



Results

The performance of the patient on the MMSE was within the normal range (MMSE: 28). The patient's performance on tests TMTA and SNST are shown in Figure 1. The second condition of TMT (B) was not completed due to patient's error, despite good clarity. Patient's performance in PD-CRS scale are shown in Table 1 and Figure 2

Discussion

The examinee's performance in the MMSE test is placed at normal levels. The qualitative analysis of errors reveals weakness to recall three words given to him when listening (withdrew the two of them) and failure to perceive and copy the visually presented shape. His performance in speed adjustment of selective attention [19] is placed at normal levels. This test measures the effectiveness of concentration, although patients with significant problems in sustained attention start with a good rate of speed but slow down towards the end of the process. [18] The patient's performance in the visual-motor tracking speed [17] is placed at levels of mild difficulties and he was unable to meet the test that examines the alternation and shift of attention. [17]. This present test is a visual-motor detection of shared attention and requires mental flexibility. According to some researchers the first part of this test detects progressive cognitive decline even in the early stages of dementia while failure to execute the second part is connected with the patient's functionality problems. [18] In this test the interviewee responded with slowness (3min 31sec) and towards the end of it he lost visual-motor coordination doing wrong pairing. This is a test of optical scanning, speed and flexibility of movement contribute to the successful attempt and besides speed attention is also involved.

The types of errors can give important information about the patient's condition [18]. This patient has made a spontaneous error (bypassed letter Z and joined 6 with Θ) and a mistake of persistence (joined 11 with 12) despite his initial good effort. In healthy people we usually don't find errors in this test. The errors are associated with frontal lesions although the views of researchers differ. Generally, the responses in the optical arrangement with complexity, the ability to maintain a sequence as well as the flexibility in rotation during the course of a current activity are clearly visible in this procedure [18].

The performance of the examinees's test in PD-CRS scale is totally placed at serious difficulty levels.The serious difficulties refer to severe cognitive impairment (<2SD). The aforementioned range is a high psychometric validity and reliability tool which is capable of detecting minute fronto-cortical deficits. [8]. Maximum patient's performance on this scale occurred at the examination of attention. His performance in working memory was good. Failure in this test has been associated with dementia [18]. His performance was also satisfactory with the spontaneous clock drawing test. This exact test involves visual-perception and visuospatial skills and recruitment vocabulary, arithmetic knowledge, working memory and executive functions. [18,20] The performance of the examinee was low in immediate recall of verbal memory subtests, delayed verbal memory recall, and verbal fluency. Demented patients make mistakes from the beginning as refers immediate and delayed recall of verbal material.

Patients with Parkinson's disease do not all show deficits in the test due to the multidimensional nature of the disease. However, the PD patients do not spontaneously use semantic strategies. [18] The patient withdrew five words at the first attempt, the second time 4, and the third time 5, while at the third he committed a mistake of intrusion. In the delayed recall he managed four words. It is verified that there is no learning curve (recall from the beginning fixed number) and no problem seems with withdrawal (delayed recall). [18] The verbal flow test is quite sensitive in patients with Parkinson's disease deficits. Generally, the impaired verbal power has been associated with frontal damage. [18] In the verbal flow switching test the examinee did not respond at all. Specifically, he was unable of making any switch while responded to only a portion of the test. The test involves switching phonological and semantic ability. Patients with PD have greater difficulty with semantic fluency. This patient responded to the phonological requirements better than the semantic one.

However, he could not make any switch. The switch is a complex skill that includes the capabilities of cognitive flexibility and mental shift [21] All the above PD-CRS tests are subcortical tests. In cortical tests the examinee performed satisfactorily. In the copy clock test he performed very well. This test examines the visuospatial perception and organization. Patients with PD perform abnormally low in such tests, but with a wide variability among individuals [18]. In Juxtaposition / naming we examine the ability of naming objects; his performance in this subtest was satisfactory. His mistakes here were a result from inability to find a suitable word or inability to recognize the image. Generally, patients with dementia show deficits in this test [18] Having the performance of the examinee's tests and the bibliography, we can conclude that he totally presents cognitive impairment indications at a serious difficulty level. In particular, it appears that the features of simple attention and visuospatial skills are placed at normal levels. The features showing deficits are the speech, memory, and the complex executive functions as well.

One of the limitations of this study is that the PD-CRS refers to the total score and not the individual functions under consideration. It would be a useful reference for further research in future, as refers the purposes of diagnosis and/or differentiation in diagnosis from dementia due to Alzheimer or other psycho-emotional conditions that affect cognition[18]. The comparison of individual performance with regulatory norms is necessary to determine deficiencies and abilities to the direction of intervention and the choice of treatment strategy as well. To a degree, it also specifies and predicts the course of the disease for the patients themselves as well as their carers. [3]

Another limiting parameter is the limited scale of visuospatial functions. The patient had a good performance in the above tests but there were qualitative deficits which may need further investigation. They refer to the study about the evolution of the disease both for other works and the same patient in the future as well. Also, this patient was not given mood questionnaires due to limited time. In future examination during the progressive course, it would be useful to administer questionnaires related both to detect the mood and to exclude the influence of mood in the general cognitive status [20] In this study, the memory tests were those included in PD-CRS scale. In future examination of the patient, it would be useful to give more memory tests in order to study the course of mnemonic errors quantitatively and qualitatively alike.

Despite the limitations and observations, this study highlighted several of the patient's deficits with early onset of PD, but also several ability features of the patient which are useful both for diagnostic purposes and to the therapeutic direction.

The authors report that they have no conflicts of interest

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Nanoceria attenuate amyloid beta peptide- and zinc oxide nanoparticle-induced cytotoxicity in SH-SY5Y cells

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Keywords: Alzheimer disease - Amyloid beta-peptides - Cell death – Cerium – Zinc oxide

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Abstract

Alzheimer's disease is a chronic neurodegenerative disease and the most common form of dementia in elderly. About 35 million people worldwide are diagnosed with the disease. To date, there is no cure for the disease. The current available treatments are mainly to treat symptoms associated with the disease. Therefore, finding a treatment to cure, or at least halt the disease progression is necessary. Progressive memory impairment and cognitive decline are the major symptoms of the disease. Alzheimer's disease is associated with the presence of senile plaques in the brain areas responsible for learning and memory. Senile plaques are extracellular deposits of insoluble amyloid beta (Aβ) peptide. Aβ peptide is toxic and has been shown to cause death in many cell types including SH-SY5Y cells. Aβ peptide-treated SH-SY5Y cells are a popular Alzheimer's disease model for in vitro studies. Furthermore, Aβ aggregation can be induced by zinc. Nanoceria has been demonstrated to have potential anti-oxidant and anti-apoptotic properties. **Objective:** We hypothesized that nanoceria can alleviate Aβ peptide- and zinc oxide (ZnO) nanoparticles-induced death in SH-SY5Y cells. **Materials and Methods:** Cell viability was quantified using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. **Results:** We found that the cell viability was reduced to ~80% and ~50% when treated with $A\beta_{25-35}$ (50 μM) and ZnO-nanoparticles (50 μg/ml), respectively, for a day. Nanoceria (25 - 100 μg/ml) is able to alleviate Aβ peptide- and zinc oxide nanoparticle-induced cell death in a dose-dependent fashion. **Conclusion:** Our results suggest that nanoceria could potentially be used for the treatment of Alzheimer's disease.

Introduction

Alzheimer's disease (AD) is the most common form of dementia in elderly people [1]. The disease is characterized by the gradual loss of cognitive function and memory due to neuronal death in the brain [2]. The two pathological features of Alzheimer's disease are the presence of neurofibrillary tangles and accumulation of senile plaques in the brain [3]. Senile plaques are extracellular deposits of Aβ peptide [4]. Aβ peptide is derived from the sequential proteolytic cleavage of amyloid-precursor protein (APP) by β- and γ-secretases [5]. The most common isoforms of Aβ peptide are $A\beta_{1-40}$ and $A\beta_{1-42}$. $A\beta_{1-42}$ is more neurotoxic than $A\beta_{1-40}$ [6]. Although the precise cause of Alzheimer's disease remains unknown, it is widely accepted that Aβ peptide plays an important role in the development of Alzheimer's disease. Aβ peptide could induce activation of apoptotic pathway, elevation of oxidative stress and impairment of mitochondrial function [6].

Zinc is an essential nutrient and co-factor for many enzymes in the body [7]. The brain contains the highest level of zinc within the body. Zinc is found in the presynaptic neurons and may serve as signalling substance in neurotransmission [8]. Therefore, zinc homeostasis is important in maintaining the normal brain function. Zinc dysregulation has been associated with the neuropathogenesis of Alzheimer's disease [9]. For example, high levels of zinc were found in senile plaque [10]. Aβ binds to zinc and forms aggregates [11]. It has also been reported that Aβ peptide deposition in transgenic mice can be inhibited with a zinc chelating substance [12].

Application of nanotechnology to biological systems provides novel opportunities to intervene the pathological process of disease. Nanoceria or cerium oxide (CeO_2) nanoparticles are a rare earth metal oxide and are widely used as a catalyst in many industrial applications because of its potent-redox reactions [13]. Nanoceria serve as a free radical scavenger and protect cells from death due to oxidative stress [14]. Since Alzheimer's disease is associated with free radical-induced neuronal dysfunction and death, nanoceria may ameliorate the disease progression.

In this study, we aimed to examine the protective effects of nanoceria on Aβ- and ZnO nanoparticle-induced cytotoxicity in human neuroblastoma SH-SY5Ycells. SH-SY5Y cells have been extensively used as a model in studying pathogenesis related to Alzheimer's disease [15-18]. The effects of nanoceria on Aβ peptide- and ZnO nanoparticle-induced cell death were determined by MTT assay. To the best of our knowledge, this is the first study to examine the potential interaction between nanoceria and ZnO nanoparticles in a neuronal cell line.

Materials and methods

Materials

SH-SY5Y human neuroblastoma cell line was purchased directly from American Type Culture Collection (ATCC; Manassas, VA, USA). Dulbecco's modified Eagle's medium (DMEM) and fetal bovine serum (FBS) were Gibco® products of Life Technologies obtained from Biodiagnostic (Malaysia) Sdn Bhd. $A\beta_{25-35}$ was obtained from Enzo Life Sciences (Farmingdale, NY, USA). CeO_2 and ZnO nanoparticles, and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were bought from Sigma-Aldrich (Malaysia). 25 cm^2 tissue culture flasks were Nunc™ products obtained from Fisher Scientific (Malaysia). 96-well Corning® microplates were purchased from FC-Bios (Malaysia) Sdn Bhd.

Cell culture
SH-SY5Y cells were propagated and routinely cultured in DMEM supplemented with 10% FBS at 37°C in a humidified atmosphere with 5% CO_2 in 25 cm^2 tissue culture flasks. Cells were plated at a density of 5 x 10^4 cells per well on 96-well microplates and were maintained a similar culture condition in DMEM containing 1% FBS for an overnight before subjected to experimental treatments.

Stock preparation
SH-SY5Y cells were treated with indicated concentrations of $A\beta_{25-35}$ or ZnO nanoparticles, in the presence or absence of nanoceria for 24 or 48 hr. Each treatment was performed in triplicate and each experiment was repeated three to six times.

Experimental design
SH-SY5Y cells were treated with indicated concentrations of amyloid beta (25-35) or zinc oxide nanoparticles, in the presence or absence of cerium oxide nanoparticles for 20-24 hours. Each treatment was performed in triplicate and each experiment was repeated three to six times.

MTT cell viability assay
The protective effect of compounds on cell viability was assessed by using MTT conversion assay [19]. The cells were incubated with MTT solution (final concentration of 0.5 mg/ml) in the dark for 4 h at 37°C. The dark-blue formazan crystals formed in intact cells were solubilized with isopropanol solution acidified with 0.1 N HCl. The optical density of each well was measured with a Bio-Rad microplate reader at the test wavelength of 570 nm. The absorbance values of the reference wavelength of 690 nm were then subtracted from the results. Optical density is directly proportional to the number of living cells in culture. The untreated control values were set to 100%. The data obtained were then expressed as percentage of viable cells relative to the untreated control group value.

Statistical analysis
Data analysis was performed using GraphPad Prism 6 software. The data were expressed as mean ± SEM. Statistical differences among experimental groups were evaluated by performing one-way analysis of variance (ANOVA), followed by the post-hoc Newman-Keuls multiple comparison test.

Results

The viability of SH-SY5Y cells was reduced in a dose-dependent fashion when the cells were treated with increasing concentrations of $A\beta_{25-35}$ (2 - 100 μM) for a day (Fig. 1). Significant drop in cell viability, down to ~85% of the control value, was seen when the cells were exposed to 20 μM of $A\beta_{25-35}$. As the $A\beta_{25-35}$ concentration increased to 50 μM, the SH-SY5Y cell viability was further reduced, with the mean value down to ~80% of the control value (Fig. 1, Fig. 4A). When the cells were treated with the same concentration of $A\beta_{25-35}$ for two days, the viability was reduced to ~70% (Fig. 4B).

Similarly, the cell viability also dropped in a dose-dependent manner when SH-SY5Y cells were treated with increasing concentrations of ZnO nanoparticles (25 - 400 μg/ml) (Fig. 2). Almost all SH-SY5Y cells were dead when the cells were exposed to 400 μg/ml of ZnO nanoparticles. A dose-response curve was plotted to determine the IC_{50} value of ZnO nanoparticles in causing cell death (Fig. 2B). IC_{50} value obtained from the dose-response curve fitting is ~50 μg/ml.

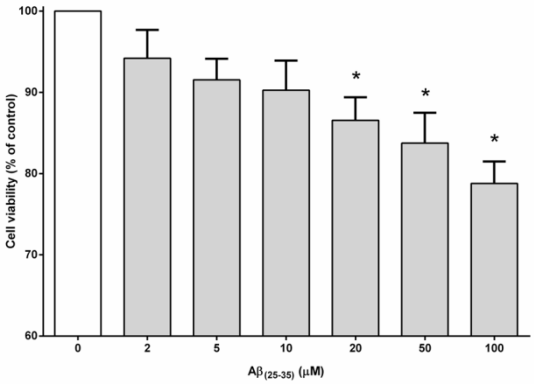

Figure 1. Aβ25-35 induces cell death in SH-SY5Y cells. To evaluate the effects of Aβ on cell death, SH-SY5Y cells in culture were pre-treated with 2 - 100 μM Aβ25-35 for 24 hr at 37oC. Number of viable cells was quantified by MTT assay. The control was set to 100% survival. Data are means ± SEM. Data were analysed using one-way ANOVA and Newman-Keuls' test. *p < 0.05, **p < 0.01 and ***p < 0.001, compared with the control group.

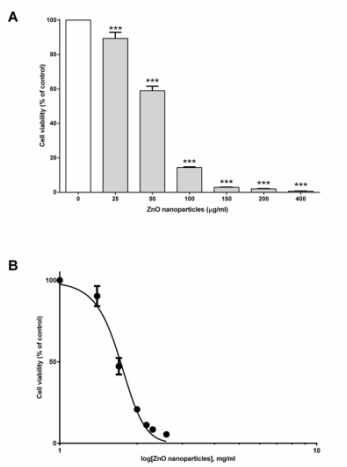

Figure 2. The effect of ZnO nanoparticles on cell viability. Cultured SH-SY5Y cells were exposed to increasing doses of ZnO nanoparticles from 25-400 μg/ml for 24 hr at 37oC. (A) Cell viability was measured by MTT assay. The control was set to 100% survival. Data are means ± SEM. Data were analysed using one-way ANOVA and Newman-Keuls' test. ***p < 0.001, compared with the control group. (B) A dose-response curve was plotted to obtain the IC50 value.

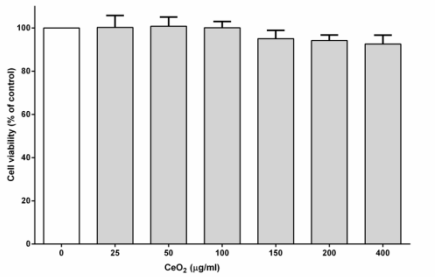

Figure 3. The effect of nanoceria on cell viability. SH-SY5Y cells were treated with various concentrations of nanoceria (CeO2) from 25 - 400 μg/ml for 24 hr at 37oC. Number of viable cells was measured by MTT assay. The control was set to 100% survival. Data are means ± SEM. Data were analysed using one-way ANOVA and Newman-Keuls' test.

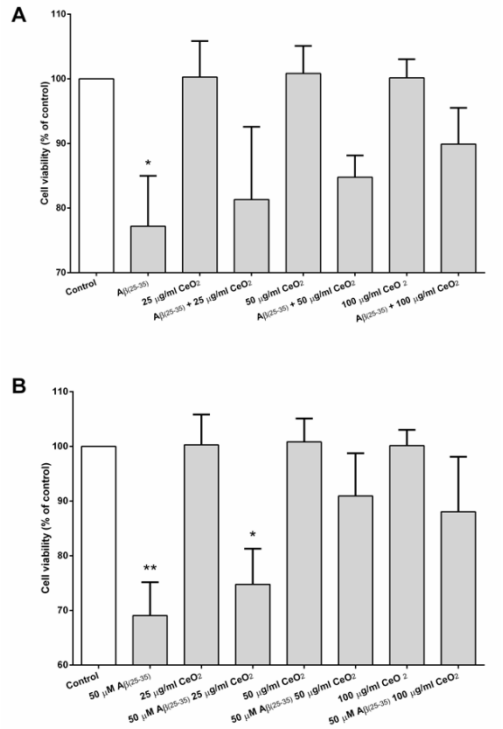

Figure 4. Nanoceria protect against Aβ25-35-induced cell death. SH-SY5Y cells were incubated with 50 μM Aβ25-35 in the absence or presence of varying doses of nanoceria (CeO2; 25, 50 and 100 ug/ml) for 24 hr (A) and 48 hr (B) at 37oC. Number of viable cells was measured by MTT assay. The control was set to 100% survival. Data are means ± SEM. Data were analysed using one-way ANOVA and Newman-Keuls' test. *p < 0.05 and **p < 0.01, compared with the control group.

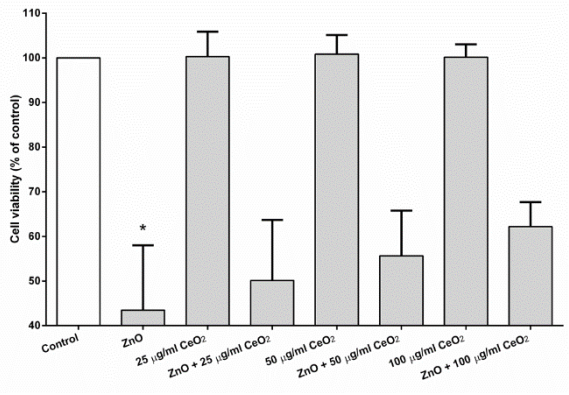

Figure 5. The protective effect of nanoceria on ZnO nanoparticles-induced cell death. Cultured SH-SY5Y cells were exposed to 50 μg/ml ZnO nanoparticles in the absence or presence of different doses of nanoceria (CeO2; 25, 50 and 100 μg/ml) for 24 hr at 37oC. Number of viable cells was measured by MTT assay. The control was set to 100% survival. Data are means ± SEM. Data were analysed using one-way ANOVA and Newman-Keuls' test. *p < 0.05, compared with the control group.

Nanoceria did not cause any reduction in cell viability up to the concentration of 100 μg/ml (Fig. 3). When the cells were treated with higher concentrations of nanoceria (150 - 400 μg/ml), only a very minor reduction of cell viability was observed. Induction of cell death with $A\beta_{25-35}$ (50 μM) for 1 day and 2 days was attenuated by the co-treatment with nanoceria (25 -100 μg/ml) in a dose-dependent manner (Fig. 4). Nanoceria (100 μg/ml) were able to restore the cell viability to ~90% of the control value. Similarly, nanoceria were able to attenuate ZnO nanoparticle-induced cell death (Fig. 5).

Discussion

SH-SY5Y is a sub-line of the original human bone marrow biopsy-derived SK-N-SH cell line [20]. SH-SY5Y cells share many characteristics of neurons, for example, the two main synthesizing enzymes unique to catecholaminergic neurons namely tyrosine hydroxylase and dopamine-β-hydroxylase are present in these cells [21]. As such, SH-SY5Y cells have been served as an excellent model for neurodegenerative diseases such as Parkinson's disease and AD. The cells together with amyloid-beta peptides have been extensively used as an in vitro model of Alzheimer's disease in studying the cellular pathogenesis of the disease [15-18]. Aβ peptide-induced neurotoxicity is thought to be a central dogma to the etiology of AD.

$A\beta_{25-35}$, consisting of 11-amino acid, is a functional fragment of full length Aβ peptide. $A\beta_{25-35}$ has been utilized in many in vitro studies due to the fact that it retains most physical and biological properties of the full length peptide. For instance, this peptide exerts high levels of cytotoxicity in both neurons and neuronal cell lines [22-25]. The toxic effects exhibited by this peptide such as neuronal death, ROS generation and lipid peroxidation are very similar to those produced by the full length peptide, $A\beta_{1-42}$ [26, 27]. $A\beta_{25-35}$ has also been reported to exhibit its toxic effects more rapidly than $A\beta_{1-42}$ [28]. $A\beta_{25-35}$ is also cheaper to produce and easier to manipulate since it is a shorter fragment of the full length peptide. All of these properties make $A\beta_{25-35}$ an ideal peptide to study the pathogenesis of Alzheimer's disease in vitro.

Here, we reconfirmed the toxic effect of Aβ peptide by treating SH-SY5Y cells with varying doses Aβ25-35. Results obtained from MTT assay showed that $A\beta_{25-35}$ diminished the viability of SH-SY5Y cells in a dose-dependent fashion which is consistent with many published reports [29-33]. Traditionally, the mechanism of cell death is classified into two distinct pathways, namely apoptosis and necrosis. Although Aβ peptide can induce necrosis in cultured rat PC12 cells [34], the major cell death pathway associated with Aβ peptide-induced toxicity in SH-SY5Y cells is apoptosis [35].

The industrial application of ZnO nanoparticles is abundant. It is widely used as an additive in many products such as rubbers, ceramics, paint and food, just to name a few of its applications. ZnO is also an active ingredient in sunscreen and topical medications to prevent or treat skin burns and irritation. The toxic effect of ZnO nanoparticles was assessed in SH-SY5Y cells. We demonstrated that ZnO nanoparticles induced the death of SH-SY5Y cells in a concentration-dependent manner. Our results are in agreement with the finding from a previous study in the same cell type [36]. ZnO nanoparticles can be dissociated into free Zn^{2+} ions. Zinc has been shown to be able to interact with Aβ peptide and induce Aβ peptide aggregation [10]. Secretases, the APP processing enzymes, are also regulated by zinc [37]. Moreover, SH-SY5Y cells express APP and β-secretase [38]. Previous studies have reported that oxidized lipids can mediate release of Aβ peptide from SH-SY5Y cells [39, 40]. Thus, it is possible that the toxicity of ZnO nanoparticles is partly mediated via interaction with Aβ peptide. Although Valdiglesias and co-workers reported that the toxic effect of ZnO nanoparticles was not due to the alteration in cell membrane integrity, they could not rule out the possibility that ZnO nanoparticles may interact with membrane-associate proteins. ZnO nanoparticles may exert its toxic effect by interacting with β-secretase, a membrane-associated protein [38]. Poorly regulated β-secretase activity could cause overproduction and deposition of Aβ peptide, which is toxic to the cells. Further studies are required to address these possibilities.

Here, we demonstrated for the first time that co-treatment with nanoceria (25, 50 and 100 ug/ml) inhibited ZnO-induced cell death in a concentration-dependent fashion, as evidenced by the increase in cell viability. A previous study has shown that ZnO induced cytotoxicity in RAW 264.7 and BEAS-2B cell lines, leading to generation of ROS and cell death [41]. Thus, the protection exhibited by nanoceria could be due to its direct antioxidant properties. In the present study, we also demonstrated that same concentrations of nanoceria protects against $A\beta_{25-35}$-induced cytotoxicity in SH-SH5Y cells. This finding is in agreement with a previous report investigating the effect of nanoceria on the survival of differentiated SH-SY5Y cells [42]. In that study, the authors demonstrated that nanoceria affect the transduction pathways associated with neuronal survival, such as ERK and BDNF signalling pathways. The mechanism underlying the protective effect of nanoceria against ZnO nanoparticle-induced cell death shall be further explored as the protection may not be solely due to its anti-oxidant properties.

Due to the size of the particles (< 100 nm), nanoceria could potentially cross the blood-brain barrier. The ability to cross the blood brain barrier is an important property for any agents to be considered for the treatment of brain-related disorders. The nano-size property together with the findings from our study suggests that nanoceria could potentially be used as a therapeutic agent for Alzheimer's disease. Furthermore, the data provided in this study will also stimulate more future research to delineate the functions of ZnO nanoparticles with regard to pathogenesis and development of Alzheimer's disease.

Acknowledgement
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The authors declare that they have no conflicts of interest.

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Primary age-related tauopathy: part or not part of Alzheimer disease?

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Keywords: PART – Tau - β-amyloid

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Abstract

In the last year, the appearance of a newly introduced term "PART", deriving from the acronyms for Primary Age-Related Tauopathy, has opened an interesting but simultaneously argumentative (challenging) discussion around the thematic of the possible mechanisms, that could better describe the pathological alterations found in Alzheimer's disease brains compared to them of old aged individuals. The group that firstly presented PART as an independent nosological entity argues that there are changes of tau aggregation in the form of neurofibrillary tangles (NFTs) in the brains of old persons, but with no evident or only mild Aβ-amyloid pathology. The main differences compared to Alzheimer's disease is, that tau histopathological alterations in PART are limited mainly in particular brain regions, thus PART involves cases corresponding to entorhinal (I-II) and limbic (III-IV) Braak stages, and as far as Aβ deposits are concerned these range from phase 0 to 2. In addition, it has been shown that there is no association between PART and ApoE ε4 allele, which in fact represents the strongest risk factor for Alzheimer's disease. In line with the above mentioned various biomarker-based clinical studies have also identified normal elderly individuals with abnormal neurodegeneration biomarkers but without abnormal brain amyloidosis. On the other hand, there is a subset of experts that support the *"continuum"* hypothesis, which actually accepts PART as a stadium in the progress of Alzheimer's disease. According to this hypothesis there is an uninterrupted evolution from tau+/Aβ- to tau+/Aβ+, hence the processes resulting in the pathological accumulation of these two proteins develop in a constant way and in a linearly proportional manner. As a conclusion, it should be emphasized the need for more profound research in the development of tau and Aβ-amyloid pathology that will allow us one day to give a definite answer to the question "PART is part or not of Alzheimer disease?"

Introduction

It was indeed a revolutionary idea the proposal by Crary and colleagues for the creation of a separate neurodegenerative disease, which was subsequently given the name PART [1]. One of the reasons that led them in such a decision was the presence among elderly normal or mild cognitive impaired persons of tau accumulation -in the form of neurofibrillary tangles-, but which was restricted mainly to structures in the medial temporal lobe, specifically the hippocampal formation and the adjacent regions. In addition, these particular cases were characterized by the absence of Aβ pathology, a finding which actually excludes them from Alzheimer diagnosis. Another motif for this initiative was the obvious need for replacement of the currently used terms of "tangle-only dementia" and "tangle-predominant senile dementia" with a more precise clinicopathological designation, since the aforementioned expressions do not correspond well to such cases, where the clinical symptomatology of the affected individuals is characterized only by amnestic cognitive changes, thus the use of the word dementia in these instances is an hyperbole. As it is well known, dementia refers to several neurodegenerative conditions (i.e. Alzheimer disease, corticobasal degeneration [CBD], frontotemporal lobar degeneration [FTLD, etc.), all of which have in common a considerable impairment in various fields of perception and intellect as well as loss of the ability to fulfill even easy tasks of daily life. On the contrary, persons who were believed to have PART did not show any of the described disturbances and consequently the term dementia should be avoided in this particular category of patients [2-5]. However, on the opposite side there are the supporters of the so called *"continuum hypothesis"*, who believe that the above described cases (which are considered as being of the recently presented neurodegenerative disease-entity [PART]) possible represent primary stages in the uninterrupted development of Alzheimer's disease process. Inspite the fact, that the regions affected either by tau or Aβ pathology follow a definite sequence and a stepwise pattern, it seems that the progression of the illness is independent of the lesion density in these areas [6]. In every case, further research needs to be undertaken, in order to be definitely clarified, whether PART represents a new neurodegenerative disease or is in fact a pre-stadium in the progression to pathologically and clinically manifested Alzheimer's disease.

Neuropathologic changes

The examination of brains, derived from individuals with PART, shows either no apparent differences compared to brains of normal aged controls or may exhibit mild to moderate diffuse atrophy of the neocortex, even with medial lobe atrophy in persons with dementia [7,8]. In the microscopic level, it is noteworthy to mention that the accumulation of neurofibrillary tangles (NFTs) in cases with PART ranges from Braak Stage I to Stage IV [9,10], but without progressing to the isocortical Braak Stages (V-VI), even in the very old individuals [11,12]. Another interesting feature in the brains of individuals with PART, who developed cognitive impairment, is the presence of extracellular so called "ghost" tangles [7,8]. However, the total absence or the minimal only deposition of Aβ plaques (Aβ phase 0-2), estimated according to grading system of Thal [13,14], chacterizes the majority of PART

cases and consecutively differentiates them from Alzheimer's disease (AD) cases, since the formation of Aβ plaques is a constant finding in the latter and also substantial for its diagnosis [15,16]. Crary et al, suggest the designation "Definite PART" for cases with Braak stage ≤4 and Thal Aβ phase 0 and "Possible PART" for those with Braak stage ≤4 but Thal Aβ phase 1-2 [1].

Clinical features

As it has been already mentioned above, the majority of cases considered as belonging to PART, show symptomatology ranging from normal to amnestic cognitive changes. Although, there are previous studies, which present cases considered as severe PART, even with associated memory loss in old aged persons [3,4], these examples need further investigation, since this clinical picture could be the result of other comorbid diseases in this particular caategory of individuals [5, 17]. Nevertheless, several other publications have already demonstrated a number of PART (in the past referred with several other names, such as "Senile Dementia of the Neurofibrillarry Tangle Type" [SD-NFT], "Tangle -Predominant Senile Dementia" [TPSD], etc.) cases with significant clinical impairment, but without any identifiable factor as the obvious cause for the diagnosed dementia [3, 18-20].

PART and SNAP

The combined application of various imaging techniques and well established neurodegeneration biomarkers have identified cases with AD-like changes but without Aβ-amyloidosis, which have been given the name "Suspected Non-Alzheimer's Pathophysiology" [SNAP] [21-28]. The most often used biomarkers of Aβ-amyloidosis are the amyloid PET and the low CSF Aβ42, whereas of AD-related neurodegeneration the high amount of tau in CSF, the brain atrophy on structural MRI and the decreased metabolism on FDG-PET, these last two in an AD-like topographic pattern [29]. The primary results, derived from the direct comparison of the cases defined as SNAP and of them characterized as PART, show a straightforward link between the atrophy of medial temporal structures and the abnormally high values of CSF tau on the one hand and the pathology of PART on the other hand [30]. Apart from these, both PART and SNAP seems to be more common in the same age group (including middle-aged to elderly individuals) [30], but also the frequency of APOE4 carriership in these two entities is significantly lower compared to preclinical AD [21, 22, 31, 27]. Last but not least, both SNAP and PART refer mainly to cases characterized by no or mild cognitive impairment and only rarely include examples of obvious dementia [32, 30].

PART as part of Alzheimer disease

In the preceding sections, there was an attempt to present in brief the characteristics and the particularities of the newly introduced entity PART, without bearing in mind the opinion of the group of researchers who consider PART as a preliminary stadium in the progression to well established Alzheimer's disease. In this part we will concentrate in this point of view and try to analyze their arguments but also to understand their skepticism in the creation of a new neurodegenerative disease-entity.

According to PART hypothesis, the amount of NFTs will reach a maximum, which corresponds to Braak stage IV, and the Aβ amyloid will not go beyond Thal phase 2, even if the persons under examination would have lived longer. Moreover, the accumulation of tau is regarded as a phenomenon that is associated with aging, whereas the deposition of Aβ amyloid is linked to AD. Consequently, the presence of Aβ amyloid in the very old persons should be excluded, while these would be affected constantly by tau. However, in a report published by Delaere and colleagues, Aβ deposits were found in twenty French centenarians, irrespective of their clinical state, regarding presence or absence of dementia. Therefore, the authors conclude that Aβ accumulation in the brain represents an "ineluctable" age-related process [33].

The *"continuum"* hypothesis accepts that the intrinsic properties, which are associated with tau aggregation, are indeed invariable and indistinguishable, when compared the early and late NFT stages. On the contrary, the PART hypothesis differentiates between age- and AD-related NFTs, since the presence of the latter, but not of the former, depends on the accumulation Aβ amyloid. Obviously, it makes more sense the use of the same term for identical inclusions, than the introduction of a new one, depending solely on an extrinsic factor, that is the presence or absence of Aβ deposits. This view is also in full correspondence with the grouping of the various neurodegenerative diseases under the broader terms "tauopathies", "synucleinopathies" etc. [6].

Furthermore, the detractors of the PART hypothesis believe that it is practical impossible to distinguish cases of AD at onset from PART with a low number of Aβ deposits, and this is due to the fact that the processes which underlie Aβ accumulation and tau aggregation seems to develop in a parallel manner, and consequently an isolated Aβ deposition is indeed an exception [34]. Another example that demonstrates the difficulty in separating "age-related" and AD-related processes, describes an hypothetical scenario in which initially the diagnosis of PART is given, because of the presence of tau in the entorhinal cortex and hippocampus. However, with the progression of the disease and the appearance of Aβ amyloid the diagnosis of PART should be reconsidered and finally replaced by AD, since the disease under question would not be anymore a "pure tauopathy". The supporters of *continuum* hypothesis wonder further, whether it is reasonable to accept the low scores of Aβ plaques compatible with possible PART, whereas the moderate and high scores only with AD [6].

Conclusions

All in all, the current knowledge does not permit us to prove, whether PART is a separate neurodegenerative disorder or it definitely belongs to the heterogenous spectrum of AD. Therefore, further studies need to be carried out in the future, and these should take advantage of all the new diagnostic and research methods (in the fields of molecular biology/genetics, pathology, imaging etc.), and also to be concentrated in the centenarians, since in this particular age-group could be possibly found the answer to the aforestated question.

The authors declare that they have no conflicts of interest.

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The effect of Risperidone, Sertraline as monotherapy and in combination with cholinesterase inhibitors on Alzheimer Disease cognitive functioning: A randomized clinical trial

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Abstract

Alzheimer's disease is a progressive neurodegenerative disorder which is characterized by the progressive decline in memory and other cognitive abilities. Behavioral and personality changes can also be present. Depression is also a neuropsychiatric aspect of Alzheimer disease. ***Objective:*** The aim of this study is to compare the effect of risperidone as monotherapy in patients with behavior problems, sertraline as monotherapy in patients with depression and with the combination of cholinesterase inhibitors on Alzheimer Disease cognitive functioning. ***Methods and Participants:*** The study comprised of 78 participants diagnosed with AD, all over fifty years old. The participants were split into 4 groups: groups A and B had everyday behavioral problems, while groups C and D had co-morbid depression. Group A was treated with risperidone 1mg daily, group B with risperidone and cholinesterase inhibitors, Group C treated with sertraline, and group D with sertraline and cholinesterase inhibitors. Baseline assessment of groups A and B was performed using the instrumental activity of daily living (IADL) scale, physical self-maintenance scale (PSMS), mini-mental examination scale (MMSE), while follow-up assessment after three and six months was only with MMSE. Groups C and D were assessed with MMSE and the Montgomery-Asberg Depression Rating for baseline assessment and follow-up after 12 months. ***Results:*** It was found that group A (treated with risperidone only) showed a statistically significant improvement in MMSE scores with respect to the baseline assessment after 6 months, An improvement not seen in group B (treated with risperidone and cholinesterase inhibitors). Groups C and D did not show any significant improvement in scores of either assessment scale. ***Conclusion:*** Risperidone used as monotherapy displayed a positive effect on Alzheimer cognitive function

Introduction

Alzheimer's disease is a progressive neurodegenerative disorder which damages the brain and is characterized by the progressive decline in memory and other cognitive abilities [1]. Alzheimer's Disease (AD) causes sensory and cognitive impairments that in later stages of the disease render the coverage of everyday life demands extremely difficult [2]. This cognitive impairment arises by the presence of dense deposits surrounding the nerve cells, as well as by twisted fibers in the nerve cells of the brain, as first described by Dr. Alois Alzheimer in 1906. Cognitive impairment also results from atrophy and synapse loss [3]. Dementia is characterized by memory deficits (amnesia) as well as impairment of either speech (aphasia), motor function (apraxia), recognition (agnosia), or more complicated functions such as working memory and problem solving, which affect a person's ability to successfully perform everyday activities [4]. Behavioral and personality changes can also be present, sometimes even before memory impairment begins [1, 5]. Even though scientists have concluded that genetic and neurochemical conditions are the most prevalent causes that lead to Alzheimer dementia [6, 7], nevertheless the causes of Alzheimer's Disease are yet to be totally discovered. [8] Sooner or later the neuronal damage affects basic body functions as walking and swallowing, resulting in around the clock personal care. Alzheimer's disease is recognized as the most common cause of dementia among the elders ≥65 years (Alzheimer's Association, 2015), with a threefold increase in the incidents for the next decades, as estimated by World Alzheimer's Report figures [9]. AD is the clinical reason for the cognitive decline in the 60%-70% of elderly patients worldwide and in the U.S.A 2,3 million people aged 65 and above are suffering from AD [10].

Many hypotheses for the cause of AD have been studied and published. Neurochemical functions altered in the brain of AD patients give guidelines for specific pharmacotherapeutic pathways. Loss of cholinesterase acetylcholine made the cholinesterase inhibitors the most common and effective therapy for AD. Their action involves the relief of several behavioral and psychological symptoms of the disorder [11, 12]. Psychotic symptoms such as delusions, hallucinations and cognitive disturbances, are evident in AD, making the institutionalization of

the patients inevitable, since professional medical care is required. For the confrontation of the psychosis in AD, atypical antipsychotics like Risperidone are used in clinical practice [13,14]

Depression is also a neuropsychiatric aspect of AD. Guilt, physical stress, anger, cognitive decline and apathy are the most characteristic depressive symptoms which accompany the course of AD in many patients: apathy in 41% and major depression in 24% of the patients [15]. Antidepressants like Sertraline, are used for the treatment of the depressive symptoms in AD and they seem to have quite satisfactory effects [16]. Studies for the efficacy of the recommended treatments have been published either presenting monotherapy results or combination therapy results. Some of them have not reached desirable results whereas some others give rise to hopeful treatment perspectives.

In our research we will try to compare the effect on Alzheimer cognitive function of risperidone as monotherapy versus risperidone in combination with cholinesterase inhibitors in patients suffering from AD and behavioral problems as well as depression. Similarly we will try to compare sertraline as monotherapy versus sertraline with combination with cholinesterase inhibitors in patients with AD and depression.

Methodology

2.1. Subjects

Eighty volunteers were recruited at first from the Alzheimer Disease Center in the City of Chania. Seventy eight (n=78; Males: n=27, Females: n=51) of them were able to finish the project. *Admission's criteria:* the volunteers should be more than fifty years old, diagnosed with Alzheimer Disease according to DSM-IV [17], baseline-assessment on Mini Mental State Examination between 15 and 29. The volunteers as well should have been subjected to computed tomography, CT exam (scan) in the last six months. Only volunteers with comorbid depression diagnosis were included in C and D groups. *Exlusion criteria*: serious gastrointestinal, nervous, hepatic, endocrine, pulmonary, cardiovascular, or hematologic disease, primary psychiatric or neurological disorder and clinically significant laboratory or electrocardiogram abnormalities.

Volunteers with everyday behavior problems, were randomly incorporated in groups A and B. Volunteers of group A (n=17; Males: n=4, Females: n=13) were administered with Risperidone, 1 mg daily. Where the dose was reckoned not well tolerated it was reduced to 0.5 mg daily. Volunteers of group B (n=13; Males: n=7, Females: n=6) were administered with Risperidone with the combination of Cholinesterase inhibitors. Where the 1 mg daily dose of Risperidone was reckoned not well tolerated it was reduced to 0.5 mg daily. The project on those groups lasted for six months. Volunteers with depression diagnosis were randomly incorporated in groups C and D. Volunteers of group C (n=29; Males: n=8, Females: n=21) were administered with Sertraline. Respectively volunteers of group D (n=19; Males: n=8, Females: n=21) were administered with Sertraline with the combination of Cholinesterase inhibitors. The project for those groups lasted for twelve months. On groups A and B we used Instrumental Activity of Daily Living (*IADL*) on baseline-assessment as well as the Physical Self-Maintenance Scale (*PSMS*). Following, we use the Mini Mental Examination Scale for baseline-assessment, after 3 months and finally after 6 months. On groups C and D we used the Montgomery-Åsberg Depression Rating Scale (*MADRS*) for baseline-assessment. Following, we use the Mini Mental Examination Scale for baseline-assessment and after 12 months.

2.2 Instrumental Activity of Daily Living

Instrumental Activity of Daily Living is an instrument adjusted to assess independent living skills. The instrument is useful in identifying how a person is functioning at the present time and in identifying improvement or deterioration over time. *IADL questionnaire* contains scales for telephoning ability, shopping, food preparation, housekeeping, laundering, use of transport, use of medicine, as well as financial behavior. There are 8 domains of function measured with the Lawton IADL scale. On Instrumental Activities of Daily Living, scores ranges from 1 (high function, independent) to 5 (low function, dependent), Overall score ranges from 8 to 31 [18,19].

2.3 Physical Self-Maintenance Scale

The PSMS is a six-item scale that measures the ratings of self-care abilities, in the areas of toileting, feeding, dressing, grooming, locomotion (physical ambulation), and bathing [19,20]. On Physical Self-Maintenance Scale, scores ranges from *1* (high function) to *5* (low function). Overall score ranges from 6 to 30, where higher scores indicate greater dependence [19].

2.4 Montgomery- Åsberg Depression Rating Scale

Montgomery and Åsberg Depression Rating Scale is a 10-item clinician-rated scale measuring severity of depressive symptoms. Items are rated on a 7-point *Likert scale* (from 0 to 6). The grades 0, 2, 4, and 6 are formulated separately for each item with behavioral examples that may increase the reliability and total score ranges from 0 to 60. A higher total score indicates more depressive symptoms [21, 22].

2.5 Mini Mental Examination Scale

The Mini Mental Examination Scale (MMSE) is a brief test formed to screen the cognitive function in patients with dementia. It is a very useful instrument in confirming the diagnosis of dementia and it is widely used in studies with patients suffering from AD, in order to follow the course of cognitive deduction [23,24]. It has been observed that AD

patients have similar scores in MMSE to demented patients but in Alzheimer's there are dysfunctions not only in memory but in other cognitive skills as well. The scores of AD patients are longitudinally more disappointing as the latest stages of the disease lead to expanded cognitive impairment [25-27]. The total score ranges from 0 to 30. A higher total score indicates better cognitive function.

2.6 Ethics

This research has the approval of the Scientific Committee of the Greek Alzheimer Society and Related Disorders and all participants provided informed consent.

Statistical analysis

A series of one way ANOVAs and t tests were employed accordingly to address study aims. For risperidone treatment regime a two way mixed ANOVA with time (baseline, 3 months, 6 months) as the within subjects variable and treatment regime (group A representing risperidone administration and group B representing simultaneous risperidone and cholinesterase inhibitors) was used to address main and interaction effects. Significance was set at $p<0.05$. Statistical analysis was performed using the software program SPSS 19 (IBMI).

Results

Basic demographic information for all four groups addressed in this study is presented in table 1. One way ANOVAs revealed no significant differences between groups concerning age $F(3,72) = 1.925$, $p = .133$ and baseline scores in MMSE $F(3,73) = .630$, $p = .598$. Assessment of daily life activity and physical maintenance with IADL and PSMS scale respectively, showed significant differences between the two risperidone treated groups (group A and B; *table 1*). Levene test was found statistical significant $F=24.802$, $p=.000$, however t test with equal variances not assumed was found statistically significant $t(27) = -2.480$, $p = .024$, with group A (mean=11.00) scoring less than group B (mean=16.31) in IADL. The same pattern was seen for PSMS. With equal variance not assumed (Levene test $F=8.829$, $p=.032$) t test [$t(27) = -2.399$, $p = .032$] showed that group A (mean=6.19) was less burdened than group B (mean=7.85). Two way mixed ANOVA revealed that the main effect of group on MMSE was not significant ($p = .968$) but a significant main effect of time on MMSE scores was found ($p = .006$). The two factors had a marginal significant interaction ($p=.047$). Simple effect analysis of time within each treatment regime revealed a significant difference only within group A ($p < .001$) but a non significant difference within group B ($p=.59$). Post hoc comparisons (Bonferroni adjusted) in group A showed significant differences only between baseline and 6 months ($p < .001$). Baseline to 3 months ($p = 231$) and 3 months to 6 months ($p = .06$) were not significant. Mean values of MMSE scores by each group over time are shown in *table 2*.

For sertraline treated patients (group C and B) no significant differences in MDRS scores were detected between the two groups, $t(46) = 1.710$, $p = .094$ (*table 1*). Pairwise t-tests between MMSE scores and scores measured after 12 months showed a significant difference for group C [$t(28) = -3.078$ $p = .005$] but not for group D [$t(18) = .917$ $p = .371$]. Comparisons between the two groups also failed to reach significance for both baseline assessments [$t(46) = -.532$ $p=.597$] and at end point [12 months; $t(46) = 1.323$ $p = .196$]. Means and SD are presented in *table 3*.

Discussion

Most of patients who suffer from Alzheimer's disease show not only cognitive deficits but also, various behavioral disturbances [28]. These symptoms lead to difficulties in the integration of the patient's everyday tasks. Also, behavioral disturbances burden more the caregivers which can increase the incidence of depressive disorders among them [29, 30]. In the latest decades, a quite large amount of elements about the neurochemical deficits underlining the neuropathological and clinical symptoms of AD, has been revealed. Though the indisputably neurochemical changes in dementia and mostly in Alzheimer's are yet to be displayed, cholinergic deficits in presynaptic components at the first stages of the disorder and loss of cholinergic neurons in the basal forebrain accompanied with a reduction of choline acetyltransferase (ACh) in the hippocampus and the neocortex, in the latest stages, made the cholinesterase inhibitors the most popular and unique treatment for AD for many decades [7,31]. Cholinesterase inhibitors help in alleviating the symptoms by restoring the *ACh* concentration in the cortex, but cause many difficulties in daily life [32]. The "cholinergic hypothesis" for AD was the first finding about the neurochemical deficits which cause the cognitive and neuropsychiatric conditions in AD [7].

The majority of the currently approved drugs used to treat symptoms of dementia in Alzheimer's disease are based on enhancing the availability of the neurotransmitter acetylcholine. When a patient needs to be administered a drug, cholinesterase inhibitors may be effective in some cases and are first-line consideration in Alzheimer's disease. However they may work better for prevention of these symptoms than for their treatment once they have emerged [5]. Many years there has been a debate for the efficacy of cholinesterase inhibitors in the management of symptoms of Alzheimer's disease. Nowadays there are available many of Ach's inhibitors and they have been considered as a landmark in Alzheimer's disease treatment. However, others argue that despite the modest improvements in scores on assessment scales, there is no significant clinical benefit [33]. Although cholinesterase inhibitors may slightly improve neuropsychiatric symptoms, they are also associated with adverse effects [34]. Today the use of cholinesterase inhibitors for the treatment of cognitive impairment in dementia is very

common, so many patients will be treated with a combination of cholinesterase inhibitors and antipsychotic drugs to improve behavioral disturbances. Despite the widespread use of this combination in clinical practice, there are not sufficient data from controlled clinical trials which evaluate the safety and tolerability of such combination therapy [28].

Table 1: Basic demographic information for all groups

	A		B		C		D	
N	16		13		29		19	
Men	4		7		8		8	
Women	12		6		21		11	
Age (years)	70.67 [53-81]	(8.56)	75.85 [67-82]	(4.58)	73.48 [53-87]	(8.58)	75.95 [67-83]	(3.99)
MSSE baseline	20.88 [10-24]	(4.05)	21.85 [14-24]	(2.91)	20.38 [14-24]	(2.82)	20.84 [14-24]	(3.31)
IADL	11.00 [8-19]*	(3.56)	16.31 [8-26]*	(7.02)				
PSMS	6.19 [6-8]*	(0.54)	7.85 [6-14]*	(2.44)				
MDRS					15.59 [2-52]	(10.49)	10.89 [2-89]	(7.05)

Mean (SD), range in brackets. MMSE= Mini Mental State Examination; IADL = Instrumental Activity of Daily Life; PSMS = Physical Scale Maintenance Scale; MADRS = Montgomery & Åsberg Depression Rating Scale. Comparisons between all four groups for age and MSSE baseline score, as well as comparison between group C and D on MDRS scores failed to reach significance. *A group vs. B group at $p < 0.05$.

Table 2: Risperidone: comparisons of MMSE scores means (SD) by therapy group over time

	baseline	3 months	6 months
group A	20.88 (4.05)*	22.25 (3.34)	23.88 (3.07)*
group B	21.85 (2.91)	22.69 (4.42)	22.31 (4.64)

Mean (SD). * Differences at $p < 0.05$ (Bonferroni adjusted)

Table 3: Means and SD values for MMSE scores for Sertraline treated patients

	Baseline		12 months	
	M	SD	M	SD
Group C	20.38	2.82	20.84	3.13
Group D	21.90	3.76	20.00	5.48

Even today, the treatment of agitation and aggression in dementia is a very controversial area, because antipsychotics are often misused as “chemical straightjackets” to calm down patients, and there is also a risk of cardiovascular episodes and death from these drugs [5]. As there are insufficient data from controlled trials that support the efficacy of antipsychotics and also because of the risk of cardiovascular episodes and increased mortality in elderly patients with dementia, they are not recommended for use in agitation and behavioral symptoms of Alzheimer’s disease. On the other hand, if patients remain untreated there are also risks such as early institutionalization and the risk for agitated and psychotic behaviors for the patient and their environment. Thus, some patients will nevertheless require antipsychotic treatment with an atypical antipsychotic. In this case, Risperidone is often preferred at very low doses [5, 35, 36]. The efficacy of Risperidone has been supported by large randomized controlled trials, which have shown that Risperidone reduces the frequency and severity of behavioral and psychological symptoms of dementia in patients with dementia [37]. From all the atypical antipsychotics only Risperidone and olanzapine currently have the best evidence for efficacy. Doses of *1.0 mg/day* of Risperidone appear to be at least modestly effective for treating behavioral disturbances and psychotic symptoms in patients with Alzheimer disease. The administration of such low doses of Risperidone reduces the incidence of extrapyramidal symptoms, although sedation remains a concern [7, 38].

In a double-blind placebo-controlled study for the efficacy of Risperidone in patients with AD and mixed dementia, the mean score in MMSE of the Risperidone-treated subjects was similar to the mean score of the total population [39]. The impacts of Risperidone, compared with the placebo subjects, were evident from the first 2 weeks of the treatment and remained stable until the end of the study. Other double-blind placebo-controlled studies in the USA, Canada, Australia, New Zealand and Europe, the Risperidone treated groups showed important improvements in their performance in MMSE and other behavioral assessment scales [40].

The most popular and effective treatment for AD in the latest decades is the use of cholinesterase inhibitors. Many studies have compared the efficacy of cholinesterase inhibitors with the atypical antipsychotics for the decrease of agitation in patients with dementia. Risperidone, which is an atypical antipsychotic, was found to be more effective than the cholinesterase inhibitor rivastigmine [41]. In a randomized double blind placebo controlled trial, there were groups of people with AD treated with both quetiapine, an antipsychotic, and rivastigmine. The reason of the quetiapine use was the high stroke risk in the treatment with Risperidone. Eventually the results of this study showed that Risperidone cannot be replaced easily, because its impacts on the reduction of psychotic symptoms in dementia are the most important of all antipsychotics [42]. However, the comparison of the effects of olanzapine, quetiapine and Risperidone for patients with AD accompanied with psychotic symptoms, showed no significant differences [43]. As far as rivastigmine is concerned, the cognitive improvements after several weeks of treatment cannot be provoked by other drugs [42]. The results of our clinical trial are in accordance with previous researches [40,41] which showed that risperidone has a positive effect in the cognitive function measured by MMSE in patients with AD.

In post-mortem studies of AD patients, reduction in serotonergic and other neurons, gave evidence for an antidepressant based treatment for the depressive symptoms in Alzheimer's dementia [7, 44]. It is important to notice that 30% to 50% of the Patients with AD display depressive symptoms (guilt, suicidal thoughts, apathy, low self-esteem). Evidence from case studies with depressive symptomatology and cognitive impairments, created the tendency to believe that depression in AD is a different disorder. However, in AD pharmacotherapy research, a combination of the traditional Alzheimer's treatment and tricyclic antidepressants present more efficacious impacts [45, 46].

In addition to the primary effects of AD in cognition, other factors associated with AD can have an impact on cognitive functioning [22]. Depression is a highly correlated factor with AD and seems to affect up to 50% of patients with AD [15]. Due to the severity of the consequences in their lives, many depressed patients with Alzheimer's disease are treated with antidepressants. Sertraline is a selective serotonin reuptake inhibitor that has been shown to have both antidepressant and anti-anxiety effects. Many clinical trials have demonstrated its efficacy in depression, obsessive-compulsive disorder, panic disorder, social phobia and premenstrual dysphoric disorder [47]. Research on the efficacy of sertraline for the treatment of depression in AD (dAD) has led to conflicting results. While some studies have shown that sertraline was not found to have a beneficial outcome on the treatment of depression in AD [48], some others demonstrate that sertraline is effective for the treatment of major depression in patients with AD [49].

Sertraline is a very common tricyclic antidepressant administered in cases of AD. In a Sertraline treatment study with patients presenting major depressive episodes and cognitive impairments, 38% of the patients totally responded to the treatment and 46% responded partially, as shown by their MMSE scores [49]. In another study 17 out of 26 patients responded to Sertraline treatment, after 12 weeks of treatment with a 200mg administration daily and MMSE measurements [50].

In studies with a combination of cholinesterase inhibitors and Sertraline, the results are very hopeful. For instance, Finkel and his colleagues, compared the effects of cholinesterase inhibitor donepezil alone in patients with AD with the effects of donepezil accompanied with Sertraline. The results showed that 60% of the patients of the combination treated group responded to the treatment, in comparison with 40% of the patients of the donepezil and placebo treated group. The effect of Sertraline treatment on cognitive performance in patients with AD is an under-researched field of study [19]. Prior studies on Sertraline treatment in patients with AD has found no cognitive advantage of Sertraline over placebo and no difference was detected between the treatment groups (Sertraline-treated and placebo-treated) in Mini-Mental State Examination [22, 49]. According to Gonzales-Salvador and his colleagues, depression in AD has been associated with strong deterioration of the patient's quality of life [51]. Moreover, as previous research highlights depression in AD causes disabilities in daily activities [26]. Consequently, in our study we hypothesized that Sertraline-treatment will have a positive impact on cognitive performance of patients, probably as a secondary benefit of depression reduction. Similarly with the previous studies [49, 22], there is also no evidence in our clinical trial that sertraline has any effect in the cognitive function of patients with AD.

Conclusion

Risperidone used as monotherapy displayed a positive effect on Alzheimer cognitive function whereas sertraline as monotherapy or in combination with cholinesterase inhibitors did not show any effect

Limitations

This research is limited because we were no able to repeat the measurement of the other scales MADRS, IADL and PSMS after the administration of the medication. We only measured the MMSE after 3 and 6 and 12 months. So our results are limited only to the cognitive function of the patients with AD and we could not evaluate the effect of the medication for the depression, the physical self-maintenance and the independent living skills.

Future Research

In future research we should evaluate all the scales (MMSE, IADL & PSMS) as baseline-assessment, after 3months, 6 months and 12 months. Because sertraline treatment on cognitive performance in patients with AD is an under-researched field of study, we should have more patients with AD treated with sertaline so as conduct a clinical trial to determine whether sertraline has any impact in cognitive function. Also in future we should include scales that measure the burden of the caregivers who play a significant role in patient's lives and treatment.

The authors declare that they have no conflicts of interest.

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Psychological disorders of caregivers of patients with dementing disorders: Increase of psychopathology and economic crisis in Greece

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Abstract

Caregivers of patients with dementing disorders exhibit high rates of psychological disorders. The prevalence of these disorders is a subject that has been examined in different populations of caregivers internationally. The percentage of these psychological disorders vary, though the anxiety and depressive disorders are the most common, affecting significant proportion of caregivers and consequently influence the quality of service providing to the patient, but also the quality of family life. **Objective:** The purpose of this study is to assess the percentage of the whole range of psychological disorders of caregivers of patients with dementia disorders in the period of economic crisis (2013-2014). **Material and Method:** 58 caregivers of demented patients assessed with a questionnaire of sociodemographic factors (age, sex, social status, education, etc.) and the Mini International Neuropsychiatric Interview (MINI 5.0.0. Greek version), a semi-structured neuropsychiatric interview, adapted to the Greek population. The caregivers were presented in the Memory Clinic of Eginition Neurological Department. **Results:** Caregivers showed high rates of dysthymic disorder, major depressive episode and generalized anxiety disorder. Specifically, 51,7% of caregivers had currently dysthymic disorder and 10,3% exhibited a major depressive episode. Also, in terms of generalized anxiety disorder, it was seen in very high rates. 65, 6% presented currently generalized anxiety disorder. No differences between sexes and SES (low and middle SES) were observed. **Discussion**: The serious increase in dysthymic disorder, major depressive episode and generalized anxiety disorder in caregivers of demented patients consists an important social problem in Greece. We consider that this phenomenon is connected to the economic crisis passing our country in recent years. It is crucial to raise awareness of specialists, so that patients and their families experience better mental health and quality of life.

Introduction

The care of demented patients is a major global issue, which is likely to grow dramatically in the next two decades, and is partly due to demographic change in the age of the population [1]. Caregiving for people with dementia has consistently been linked with psychological problems, usually in terms of caregiver burden, general psychological distress and depressive symptomatology [2]. The words 'burden', 'strain' and 'stress' are used interchangeably in research regarding caregivers (Caregivers of Dementia Patients -CDP). 'Caregiver burden' may be divided into the physical, psychological, social and financial demands of caring for someone or, alternatively, into 'subjective' and 'objective' burden, with subjective burden referring to the emotional consequences of caregiving. Mahoney et al. (2013) [ ] indicate that various factors are associated with caregiver (CG) 'burden' and 'stress', such as being female, having a poor relationship with the care-recipient (CR) and lack of social support. The sources of stress may vary according to the caregiver's own situation: spouses, being older, may experience strain due to physical or financial problems, whereas adult children may have conflicting responsibilities, such as work or children. The number of people with Alzheimer's disease (AD) and therefore the number of caregivers is increasing as the population ages. Long-term care of demented family members involves coping with severe behavioral problems including wandering, inability to communicate or recognize familiar people, and incontinence. Pearlin et al. (1990 [ ]) also distinguish the care into two categories: a) the emotional which refers to the sense of obligation of a person for the welfare of another and b) the actual provision of care, which is the behavioral expression of this obligation [3]. Given that the model survival time after the onset of dementia is eight years, caregiving has been conceptualized as a chronic stressor. As a result, CDP present psychological problems, health issues and a host of psychosomatic symptoms. Indeed, it was found that CDP receive 71% more drugs compared to the general population [4] and the family of AD patients shows very high anxiety levels [5]. More specifically, CPD's high levels of stress are associated with the need to cope with the patients' behavioral problems, their inability to communicate, and feelings of intense loneliness and loss which is comparable to the loss of a loved one. In fact, several studies have indicated that the levels of depressive symptomatology increase seriously in CDP [6].

Family caregivers provide the majority of care for people with dementia and experience significantly high levels of psychological morbidity, depression, stress and burden. The vast majority of Greek dementia patients receive care at home from family members. Caregiving at home is often a matter of obligation and not a matter of option, and this is partly due to Greek cultural factors and the absence of public nursing homes, The evidence that institutionalization may relieve families from the negative consequences of care is often confusing. Some studies support that there is no difference as far as the level of burden goes, suggesting that the emotional bond is

stronger than the physical separation [7,8]. Other research has found that caregivers are relieved when the patient is placed in a long-term care facility which might be considered a more protected environment [9]. Caregiving in family members with dementia is characterized by Mace & Rabins (1991) as a "36-hour day," due to the attention that patients need.

Burton et al. (1997) found that the more demanding the care is the more likely the CDP do not have time to care for themselves and to experience depressive symptoms, sleep disturbances, anger / aggression, agitation, burnout and occasional psychotic episodes [10]. The aggressive behavior, including violence, cannot easily be ignored by caregivers as they may exacerbate the fear and weakness of the caregiver to the patient [11, 12]. However, although caregivers endure great stress, they vary in their ability to cope effectively, and research has suggested that there are important differences in the degree to which they experience negative outcomes [8]. Thus, caregiving was linked to the onset of depressive disorders in older adults who had no prior evidence of vulnerability [13]. While dementia caregiving is clearly an extraordinarily long-term, unpredictable, and uncontrollable stressor, caregivers show considerable variability in their responses.

Strong supportive social ties appear to be a key mediator of caregivers' vulnerability to depression. Cooper, Balamurali & Livingston, (2007) in their study conclude to the fact that neither care recipient cognition, nor caregiver age and duration of caring are associated with caregiver anxiety levels. Family members who are CDP at home, often describe the experience as "perpetual stress and frustration" as propounded by Butcher, Holkup, & Buckwalter (2001), and the term CB is used most often to describe this phenomenon. The CB is associated to negative outcomes for caregivers, such as depression, illness, and poor quality of life [14, 15]. Various studies have shown that the behavioral problems of the patient are stronger predictors of grief of caregivers than cognitive and functional impairment. Additionally, chronic stress produced by the patient's behavior problems, may contribute to increased susceptibility to disease onset in caregivers [16, 17, 18, 1]. There is considerable comorbidity between anxiety and depression and most depressed caregivers are also anxious, although the converse is not true [1, 20].

Recent studies have also identified the use of escape-avoidance and confrontative coping as a predictor for worse caregiver physical health. The strategies of avoidance, denial and emotional discharge used by dementia caregivers are correlated with high levels of depression in several studies [21]. Similarly, more recent work demonstrated that depression is related to coping mechanisms and to the perceived burden reported by the caregivers [22]. It is also acknowledged that gender differences exist in caring and coping. Women, and especially wives, daughters and daughters-in-law are more likely to be affected by the caring career because of differences in their physical ability and social roles. Wishful thinking is also positively related to burden, so it is verified that since women use wishful thinking more frequently when compared to men, they may also report higher levels of burden [8].

In addition, several studies have found group differences across ethnicities on stress reactions, appraisals of the caregiving role, overall physical health, and level of depression. Collins and Jones reported that men experienced significant meaning in their lives through family caregiving. Moreover, while women were more likely to express verbally depressive feelings, men were more likely to use alcohol as a status response behavior [23].

Objective

There are many studies in the international literature regarding caregiving and its effects upon the CDP. In Greece, however, there is little research on this matter. This study focused on the psychological disorders of caregivers which seem to affect their mental health. As the economic crisis, in Greece, leads us to expect an increase in the incidence rates of the psychological disorders among CDP [24, 25], it is imperative to have more studies on this specific population in order to be able to provide effective prevention and intervention measures.

Material and Method

Sample

The study was descriptive and cross-sectional. We examined 58 caregivers of demented patients who visited the Memory Clinic of the Neurology Department of the University of Athens from January 2013 to February 2015. In particular, the sample consisted of 19 men and 39 women with an average age of 62.1 years; 39 subjects were spouses; 16 individuals were sons and daughters of demented patients, and 3 subjects were brothers. Subjects were given a questionnaire on sociodemographic parameters (age, sex, socioeconomic status, education, relationship with the patient) and the semi-structured psychiatric interview MINI-International Neuropsychiatric Interview [26]. The interviews lasted about 45 minutes, while the incidence of psychiatric disorders analyzed by statistical analysis (SPSS 18.00).

Data Collection Instruments

MINI International Neuropsychiatric Interview (MINI)

The semi-structured psychiatric interview MINI International Neuropsychiatric Interview (MINI) has been applied to patients. This instrument has been developed in France and the US. It explores 17 disorders according to DSM-III-R. For each disorder, one or two test questions exclude the diagnosis when found negative. Also, it is designed as a brief semi-structured diagnostic interview (DSI) for the major Axis I psychiatric disorders and symptoms caused by organic cause or alcohol use, drug use in DSM-IV and ICD-10. The validity and reliability of

the research has been accomplished comparing the MINI interview with the structured clinical interview (Patient Edition for DSM-III-R (SCID-P) and structured diagnostic interview designed by the World Health Organization for the interviewers for the CDI-10 (Composite International Diagnostic Interview-CIDI). The results of these studies show that MINI has been proven to provide high validity and reliability score, and can be administered in much less time (on average 18.7 ± 11.6 minutes, median 15 minutes) than the above psychometric tools.

A questionnaire on sociodemographic parameters (age, sex, socioeconomic status, education, relationship with the patient) was also administered. Instruments were administered to all subjects by the same experienced psychologist. An informed consent form was administered to all participants.

Results

Demographic characteristics

The sample consisted of 58 subjects (N = 58), a fortiori seniors 36 caregivers (62.1%) (Table 1), of which 19 were men (32.8%) and 39 women (67.2%) (Table 2). Regarding the level of education the majority of participants were high school graduates 31 (53.4%) (Table 3). Regarding the relationship that participants had with the demented patient cared, the vast majority were spouses 39 (67.2%) (Figure 1). Finally, on the economic status participants were at low economic range 35 (60.3) (Table 4).

Caregivers did not show a set of psychological disorders, such as suicidality, panic attacks, hypomanic episodes, agoraphobia, social phobia, obsessive compulsive disorder, posttraumatic stress disorder, substance dependence and alcohol abuse, eating disorders and antisocial personality disorder. There were, however, high rates of dysthymic disorder, major depressive episode and generalized anxiety disorder. Specifically, 37.9% of caregivers had dysthymic disorder herein, while 13.8% had dysthymic disorder in the present and the past. Therefore, 51.7% of caregivers showed currently dysthymic disorder. As for the major depressive episode, 6.9% experienced a major depressive episode in the present, while 3.4% experienced a major depressive episode in the present and the past. Therefore, 10.3% of them experienced a major depressive episode. Also, in terms of generalized anxiety disorder, it was also seen in very high rates. 39.7% showed generalized anxiety disorder herein and 25.9% in the present and the past, so all the caregivers who showed generalized anxiety disorder were 65.6%. Comparison with the existing literature indicated multiple rates to Greek caregivers (Table 5). The above results present differences to past studies, referring to 23-85% dysthymic disorder and depression and 16-45% GAD [27] and 22, 3% depression [6]. Also in terms of demographic characteristics, we note that there are no statistical differences between men and women, or between people of moderate and low social economic status. More specifically, the difference between sexes and dysthymic disorder, major depressive disorder and generalized anxiety disorder was not statistically significant (Fisher's Exact Test p= .474, NS, p= .875, NS, p= .603, NS respectively). Additionally, the difference between socioeconomic status and dysthymic disorder, major depressive disorder and generalized anxiety disorder was not statistically significant (Fisher's Exact Test p= .945, NS, p= .834, NS p= .689, NS respectively). These data concerning differences in sex and socioeconomic status are also consistent with recent Greek study in the general population [25].

Table 1: Distribution by age

AGE

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	18-30	1	1,7	1,7	1,7
	45-60	21	36,2	36,2	37,9
	61>	36	**62,1**	62,1	100,0
	Total	58	100,0	100,0	

Table 2 . Distribution by sex

SEX

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1,00	19	32,8	32,8	32,8
	2,00	39	**67,2**	67,2	100,0
	Total	58	100,0	100,0	

Table 3.: Distribution by education

EDUCATION

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	PRIMARY SCHOOL	16	27,6	27,6	27,6
	SENIOR HIGH SCHOOL	31	53,4	53,4	81,0
	UNIVERSITY	11	19,0	19,0	100,0
	Total	58	100,0	100,0	

Figure 1.:Distribution by relation

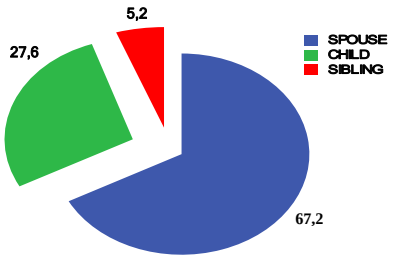

Table 4: Distribution by economic status

ECONOMIC STATUS					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	LOW	35	**60,3**	60,3	60,3
	LOW TO MEDIUM	2	3,4	3,4	63,8
	MEDIUM	21	36,2	36,2	100,0
	Total	58	100,0	100,0	

Table 5: Incidence of psychiatric disorders

Variable		Count	Column N%
MAJOR DEPRESSION	0	51	**87,9%**
	PAST	1	**1,7%**
	CURRENT	4	**6,9%**
	3	2	**3,4%**
DYSTHYMIA	0	27	**46,6%**
	PAST	1	**1,7%**
	CURRENT	22	**37,9%**
	PAST & PRESENT	8	**13,8%**
SUICIDALITY	0	58	100,0%
HYPO_MANIC_EPISODE	0	57	98,3%
	1	1	1,7%
PANIC_DISORDER	0	58	100,0%
AGORAPHOBIA	0	57	98,3%
	3	1	1,7%
SOCIAL_PHOBIA	0	54	93,1%
	1	1	1,7%
	3	3	5,2%
OBSESSIVE_COMPULSIVE_DISORDER	0	54	93,1%
	1	2	3,4%
	3	2	3,4%
POST_TRAUMATIC_STRESS_DISORDER	0	58	100,0%
ALCOHOL_DEPENDENCE_ABUSE	0	58	100,0%
DRUG_DEPENDENCE_ABUSE	0	58	100,0%
PSYCHOTIC_DISORDERS	0	58	100,0%
ANOREXIA_NERVOSA	0	58	100,0%
BULIMIA	0	57	98,3%
	3	1	1,7%
GENERALIZED_ANXIETY_DISORDER	0	20	**34,5%**
	2	23	**39,7%**
	3	15	**25,9%**

* 1=Past, 2=Current, 3=Past and Present

In a rural Greek area, the prevalence of depression in late life is high, with 39% dysthymic disorder and major depressive episode. Depression was more common among unmarried individuals, those with significant cognitive impairment, and in association with specific medical conditions [28, 29]. Concerning the prevalence of psychiatric disorders associated with the economic crisis, it was found that the economic decline had significant

influence on a person's mental health [25]. In Greece, there are no studies that have studied the psychological problems of caregivers of demented patients and there are only a few that studied the mental load (burden) experienced by [30, 8]. In contrast to these studies, the present work emphasized in the study of the whole spectrum of psychological disorders of caregivers and differentiated past and present manifestations of the diseases, in order to assess the possible impact of economic crisis on this special population.

Discussion

It is clear that CDP have a difficult task to cope with, dealing with the mood variations, the memory deficiency and the behavioral issues of demented patients, alongside with their own daily burden. In Greece, the economic crisis appears to be an additional risk factor for caregivers, who need more attention and support.

Our results showed that CDP presented high rates of dysthymic disorder, major depressive disorder and generalized anxiety disorders. The percentage of caregivers who had dysthymic disorder in the past was very small. The high percentage of dysthymic disorder (51,7%) in this study is related to patient care, but is probably also related to the economic crisis. Regarding those who had dysthymic disorder in the present and in the past we see that this figure is within the expected limits, according to the studies [6]. An impressive fact is the high percentage of caregivers (37,9%) who have dysthymic disorder at present and never had before in the past.

Regarding the major depressive episode, the percentage of caregivers who had major depressive episode only in the past (1.7%) and lifetime (3,4%) was small. On the contrary, we observe increased rates of this disorder in the current life of the caregivers. High rates of dysthymia and depression in our sample are not accompanied by suicidality. This finding may be due to the fact that caregivers feel responsible for the patient. and they may well be suffering from depression, but they do not abandon life and therefore do not abandon the patient. Regarding generalized anxiety disorder, we saw increased rates at present (39, 7%) and lifetime (25,9%). Generalized anxiety disorder was very high in caregivers.

Therefore, the results show an alarming increase in rates of dysthymic disorder and generalized anxiety, which are also highlighted by the caregivers' own reports. CPD often after the interview complained for poor psychological health, economic difficulties (decrease pensions, job loss, unemployment). They mentioned lack of "future" and low expectations for better economic and professional future, especially for sons and daughters. At the same time, they reported lack of desire for social relationships and intense grief, because they could not offer more to their partner or their parent. Spouses of demented patients also reported being very often unable to offer to their mate or their grandchildren a small gift on special occasions.

In contrast to other research findings, in our study there were no differences between men and women, concerning the occurrence of psychopathology and there was also no difference between middle and low economic level. This suggests that caring for dementia is a concern for both men and women, as well as for different socioeconomic level. These findings may be related to the economic crisis, taking into consideration that earlier studies on the quality of life of relatives and (CB), showed that women are more occupied with the patients and lower economic status caregivers are worse. Previous research has also shown that female caregivers are worse than their male counterparts, reporting higher levels of depressive and anxiety symptoms and lower levels of subjective well-being, life satisfaction, and physical health than male caregivers [31], findings.

Moreover, spousal caregivers of individuals with dementia have a high risk to develop a mental disorder. Indicators related to the caregiver's mental health rather than environmental stressors, such as patient characteristics or interruption of caregivers' daily activities predict disorder onset and can be used to identify caregivers for whom supporting preventive interventions are indicated. In addition, spousal caregivers at risk of clinical depression and caring for a spouse with significant cognitive impairment and physical care needs, are more likely to engage in harmful behavior towards their loved one [32] with higher levels of hostility than non caregivers [33].

At the same time, other studies identified other parameters that affect caregivers' self-care, because they lack the time and energy to attend personal health issues, to prepare proper meals or to exercise. About six in ten caregivers in a national survey reported that their eating (63%) and exercising (58%) habits are worse than before. Spousal caregivers who provide 36 or more hours per week of care are slightly more likely to smoke and consume more saturated fat [34] as it is shown in the current study, dealing with individuals with eating disorders (bulimia).

Additionally, stressful caregiving situations may also lead to harmful behaviors. As a response to increased stress, caregivers are shown to have increased alcohol and other substance use. Several studies have shown that caregivers use prescription and psychotropic drugs more than non caregivers [35], fact that has not emerged in this study.

Caregivers, as mentioned above, did not show a series of psychopathological events as suicidality, panic attacks, hypomanic episodes, agoraphobia, social phobia, obsessive compulsive disorder, posttraumatic stress disorder, substance dependence and alcohol abuse, eating disorders and antisocial personality disorder, as other studies indicate. This finding suggests that caregivers used to have a spectrum of mental health within the normal limits.

An important aspect of this study is that for the first time in Greece the psychopathology of CDP was studied with a semi-structured interview that covers the whole range of disorders-- from anxiety to psychotic disorders. Also, the population studied, was assessed both for present and past psychopathology. Such an

assessment has not been conducted in other studies which have focused only on present psychopathology of caregivers without taking into account their personal history of mental disorders.

One limitation of the study concerns its small sample. Another issue relates to the fact that we cannot make comparisons, given that there is a great lack of similar studies in the Greek population.

Overall, it is really important to intensify the caregivers' psychoeducation, and to provide therapeutic services (e. g. group therapy) and opportunities for CDP. Such services should be available in every Memory Clinic and public structures for dementia patients. Psychoeducation can include extensive briefing of the onset, progression and characteristics of the disease, signs of decline, prevention of risk situations, possible drugs' side-effects as well as issues of daily living activities. Such issues are homecare, pharmaceutical treatment, cooking, shopping, telephone use and self-preservation issues such as eating, dressing-up and going to the bathroom. Family caregivers' group therapy consists of psychological support for anxiety and depression, realistic control of future expectations, reduce of guilt and realization of the severity and common character of other people's problems as well.

Several studies indicate that fatigue and stressful life events such as, economic debt, are related to panic attacks and generalized anxiety disorder, highlighting financial difficulties in caregiver groups. Our study shows the impact of economic crisis to the caregivers' resilience, contributing as well as several studies to the connection between burden and psychological problems [2].

As a result, the significance of the study of psychological problems in populations similar to our sample emerges crucial. The results of the surveys conducted in Greek general population indicated that the economic decline, especially in 2008-2009 seems to be parallel to the appearance or deterioration of psychiatric disorders. The prevalence of psychiatric disorders associated with the economic crisis, concludes to the fact that the economic decline has significant influence on a person's mental health. In Greece, there are no studies concerning the psychological problems of caregivers of demented patients and there are only a few that studied the mental burden experienced by caregivers [30, 8]. The present study emphasizes the presence of psychological disorders among CDP and the impact that the economic crisis has on this particular population.

Efforts to identify and to treat caregiver psychological disorders need to be multidisciplinary and focus on multiple risk factors simultaneously [36]. Finally, it is important to continue the research conducting longitudinal studies regarding factors that contribute to the psychological burden of caregivers. .

The authors declare that they have no conflicts of interest.

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A neuropsychological exploration of Juvenile Myoclonic Epilepsy

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Keywords: Juvenile myoclonic epilepsy - Executive functions - Cognitive assessment - Motor programming - Frontal assessment battery

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Abstract

Aims: Neuropsychological research in the past few years has been exploring the cognitive function of epileptic patients. A number of investigations are looking at the epileptic syndrome of Juvenile Myoclonic Epilepsy (JME). While some detect broad cognitive impairment, others focus on executive function and others argue that there is no significant cognitive impairment for this particular epileptic syndrome. The aim of the present study is the neuropsychological evaluation of JME patients with cognitive function tasks that place emphasis on executive functioning. **Methods:** 15 patients with JME and 15 healthy controls with no significant differences in age, gender or level of education completed a cognitive battery of IQ (short version of WAIS-III), memory, attention and executive function tasks. The later included the tests of verbal fluency, Tower of London, Stroop and the Frontal Assessment Battery (FAB). It was explored whether factors such as duration of illness, time since last seizure, age of onset, years of education, age, medication and gender have any relation to cognitive performance. **Results:** Patients with JME performed significantly lower than the control group in verbal fluency, the motor programming subtest of FAB, the second (reading) subtest of Stroop and the Vocabulary test of WAIS-III. For the patient group years of education have a significant positive correlation with performance on a broad range of cognitive tasks, including IQ tests. **Discussion:** Impairments on verbal fluency and motor programming for JME patients are in agreement with previous findings. These functions are both related to functions mediated by the median thalamus nuclei. The FAB test could be used as a useful diagnostic tool in JME. Impairments on the Vocabulary test of WAIS-III and the second (reading) subtest of Stroop may reflect problems in word processing for the JME patients. Further research is needed both to determine whether these patients present learning difficulties or not and to clarify the role of education on the progress of the disease. It is possible that a neuropsychological intervention at the onset of the epileptic syndrome as well as during the course of the disease may help in rehabilitation and protection from JME.

Introduction

Juvenile Myoclonic Epilepsy (JME) is part of a broader group of epileptic syndromes named Idiopathic Generalised Epilepsies (IGE). It is often characterized by genetic predisposition with an age of onset between 8 and 20. Janz and Christian [1] were the first to describe the syndrome which includes myoclonic seizures, generalized tonicoclonic seizures after awakening and to a lesser degree absences. It is usually accompanied by normal intelligence, normal visual assessment of the brain by structural Magnetic Resonance Imaging (MRI) and a family history of similar seizures [2].

The largest part of research activity around JME can be distributed in three different areas: the neuropsychological, the cognitive and the behavioural. The first is mainly concerned with experimental paradigms of novel neuro-imaging techniques for the detection of subtle structural and histological changes in the brain. Cortical disorganization, frontal lobe impairment, dysfunction of the thalamus and other sub-cortical structures appear to be implicated in the creation of epileptic seizures and frontal cognitive disabilities often encountered in JME. Positron Emission Tomography (PET) detects changes in the metabolic activity of the cortex and thalamus [3-5], volumetric MRI reveals structural abnormalities in the cortical gray matter of the frontal region and the thalamus [6-8], while Proton-Magnetic Resonance Spectroscopy (Proton-MRS) shows pathological changes of the neuronal tissue in the same brain areas [9, 10]. JME appears to be a thalamocortical network epilepsy with the frontal lobes playing an important role and several other sites of dysfunction [11]. Cognitive research focuses on the frontal lobe function of the patients [12, 13]. Most investigations reveal frontal dysfunction [14-21] while others suggest a broader cognitive impairment [22]. It has, also, been suggested that there is no significant cognitive impairment in this patient group [23]. Recently a meta-analysis of the results so far concludes that contrary to current thinking a specific executive dysfunction for JME patients is not verified [24]. Most attempts use a limited number of participants [12, 18, 21, 23], although a few have had somewhat larger samples [14, 20, 22]. Conclusions so far point towards an executive functions impairment for this patient group, however, great variability is found even in the cognitive performance of patients within the same experimental paradigms. Behavioural research focuses on the personality problems [25,-27]. It has been argued that the methods used so far are mainly psychiatric evaluations of personality disorders and therefore are not entirely appropriate for detecting such problems in epilepsy [28]. Although findings are controversial, there seems to be an agreement that a mild frontal lobe behavioural syndrome may characterize the disorder [29-30].

In all three areas of enquiry, besides the limited number of data available, most conclusions point towards a

neuropsychological modelling of the disease that can encompass anatomical, neurochemical, cognitive and behavioural brain processes. Such a model of JME can eventually provide a better understanding of the problems encountered in the disorder and the development of therapeutic interventions. It may, also, be informative on the brain mechanisms of executive functions.

The present research attempt focuses on the further exploration of frontal cognitive functions of JME patients as these are assessed by cognitive neuropsychological tasks. The goal is the detection of possible cognitive impairment in this patient group and possible factors that influence this impairment. As mentioned above, although most research attempts so far detect cognitive impairment, this is not confirmed by all investigations [23, 24]. Also, there seems to be a great difference in the cognitive performance between patients within the same experimental paradigms. Thus, further exploration of the issue and a more careful assessment of the results so far is needed.

A battery of cognitive tests is used that assesses memory, attention, speed of processing and executive functions. An emphasis is placed on measurement of executive functions by choosing attention, memory and speed of processing tests that are also related to executive functions along with "classic" frontal functions tests such as the Tower of London. We hypothesize that in most tests JME patients will score lower than normal controls with a greater impairment on executive functions tasks. Also, a number of factors are evaluated in terms of their relation to cognitive performance. According to previous research [22] it is hypothesized that the educational background will have a significant effect on cognitive performance, while other disease-related factors such as duration of illness and time since last seizure will not have such a marked effect [20, 22].

Methods

Participants: Research participants included patients with Juvenile Myoclonic Epilepsy (n=15). They were recruited from the Laboratory of Clinical Neurophysiology and the outpatient clinic of the 1st Neurological Clinic in General Hospital AHEPA, Aristotle University of Thessaloniki (AUTH). Selection criteria for the patients included: a) chronological age between 17 and 66 years, b) educational background from elementary school and above, c) normal intelligence measured with Weschler Abreviated Scale of Intelligence (WASI), d) diagnosis of JME according to the International League Against Epilepsy (ILAE) [2] on epileptic syndromes, e) no other medication used except the antiepileptic medication, f) no other neurological disorder, g) normal clinical MRI (i.e. no structural lesions), h) no psychiatric disorder, j) no substance abuse, k) no other developmental disabilities, l) no significant difference concerning nicotine and caffeine intake in the last 24h than usual.

The final number of participants was determined by the availability of appropriate patients at the Laboratory of Clinical Neurophysiology and the 1st Neurological clinic of general hospital AHEPA, AUTH and the willingness of the patients to participate. JME patients were contacted, informed about the research project and invited to participate. Approximately forty thirty patients were contacted. Sixteen patients accepted and went through the experimental procedure. One participant was excluded because Greek was not her first language.

Control participants (n=15) were healthy volunteers that did not differ significantly in terms of age, educational level and sex from the research participants. They had no history of: a) epileptic seizures, b) diagnosed neurological disease, c) brain lesion, d) developmental disorder, e) substance abuse, f) use of medication that may affect cognitive functioning and g) no significant difference concerning caffeine and nicotine intake in the last 24h than usual. Eighteen control participants were recruited and went through the experimental procedure. One was excluded before completing the neuropsychological battery because of having difficulties in task completion. Finally fifteen were selected in order to have the two groups matched in terms of age, sex and educational background.

Experiment

The experiment took place at the Laboratory of Clinical Neurophysiology at AUTH under the supervision of the director, neurologist of the laboratory. Both JME patients and healthy controls were invited in order to measure their performance in a neuropsychological battery of tests. During the patients' visit at the laboratory all neuropsychological testing were completed along with a questionnaire on demographics and information regarding their pathology (e.g. history, clinical features). One patient, for practical reasons, went through the experimental procedure outside the facilities of the Laboratory. A similar room was used, under similar conditions, that were appropriate for the conduction of the experiment. In the same way healthy controls were measured in different locations always controlling the conditions in order to keep them similar to those at the Laboratory and appropriate for the conduction of the experiment. The neuropsychological battery was comprised of several tests that were presented in a sequential order. The battery was completed in one or two visits depending on the time taken by each participant and the time they had available. Time of completion varied approximately between 2h and 3½h. Data selection and recording were completed under the supervision of two neurologists members of the staff at the laboratory.

Neuropsychological evaluation

Initially a brief presentation of the study, the goals and the experimental procedure was conducted with all possible participants. It was made clear from the beginning that any participation would be voluntary and whoever did not wish to participate was able to refuse. A brief explanation of the neuropsychological battery and of the process of

completing it was done with all the participants. The time needed (at least two hours) was made known to the participants. A date and time were chosen in order to complete the experimental process. A quiet room was selected with a desk, chairs and everything that is necessary for the conduction of the experiment (questionnaire forms, paper and pencil, clock, special constructions for the various tasks, special forms for recording the participants performance). The neuropsychological evaluation would start with completion of the questionnaires on demographic data and medical history. It was explained to the participants that all information were protected and that it would be used anonymously for research purposes only.

Rational for measure selection:
Executive functioning was measured by the tasks of verbal fluency, the Stroop test, the Tower of London test [31] and the Frontal Assessment battery (FAB) [32]. The last measure was chosen in order to provide an extra measurement of frontal functioning that is not typically used with this patient group and because it includes a measurement of motor programming, a function relevant to action programming which has been reported to produce a provocative effect of epileptic activity in this patient group [33-37]. Visual memory was, also, measured by the Rey-Osterrieth Complex Figure test [31], working memory was evaluated by the Digit Span test (Wechsler Adult Intelligence Scale-Third Edition, WAIS-III) [38], attention was tested with the Digit Symbol task (WAIS-III) [38] and processing speed was assessed by the Trail-Making test [31]. Tests that evaluate functions different than typical executive functions were, also, chosen. The purpose of this was to achieve a more global assessment of cognitive functioning of the patient group and at the same time to explore whether any detectable impairment on executive functioning might be specific to these skills or part of a more widespread cognitive impairment. At the same time, the specific tests on attention, memory and processing speed were used because of their relation and sensitivity to executive functioning, since it has been argued that this patient group has a marked impairment in executive skills [14,21]. An evaluation of intelligence was also conducted as it is measured by four subtests of WAIS-III [38], Vocabulary, Similarities, Block Design and Matrix Reasoning. These subtests were employed since they are the ones that the short version of WAIS-III uses (WASI).

Intelligence Quotient
The four subtests of WAIS-III were used. Guidelines and procedure were followed as described in WAIS-III. A score for each subtest as well as a total score were calculated.

Attention and Speed of Processing
A Greek version of Trail Making A and B was used. Digit Symbol was conducted as presented in WAIS-III.

Memory
Digit Span was conducted as presented in WAIS-III. The Rey-Osterrieth Complex Figure test was conducted with the condition of delayed recall [31].

Executive Functioning
Verbal Fluency was assessed by the 1 minute tests of phonological fluency and semantic fluency [31]. A total score was calculated by the sum of the two scores. The Stroop test was conducted in three parts, color naming, reading and the interference condition. In each part four scores were calculated: time of completion, number of uncorrected errors, number of corrected errors and total number of errors [31]. The Tower of London test was conducted in the standard procedure described by Krikorian et al, (1994) [31]. A Greek version of the Frontal Assessment Battery was used.

The order of the presentation of the tasks during the neuropsychological battery was as follows: 1) Vocabulary (WAIS-III), 2) Similarities (WAIS-III), 3) Block Design (WAIS-III), 4) Matrix Reasoning (WAIS-III), 5) Trail Making A and B, 6) Digit Symbol, 7) FAB, 8) Rey-Figure (1st recall), 9) Digit Span, 10) Verbal Fluency and Rey-Figure (delayed recall), 11) Stroop, 12) Tower of London. The time of completion for the neuropsychological battery varied from 2 to 3 and ½ hours depending on the pace of the participant.

Statistical analyses
Data analyses was performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, U.S.A.) for Windows, version 20. The quantitative data were recorded as mean and standard deviation when they were normally distributed and as median and interquartile range (IQR) when they were not normally distributed. Qualitative data were recorded as frequencies. A comparison for the demographic variables for both groups (JME patients and controls) was performed mainly with the help of descriptive statistics. Because the two groups were controlled in terms of age, gender and level of education in order to compare the performance on the different neuropsychological tests for the two groups the t-test for dependent samples was used when the distribution of the data was normal and the Wilcoxon Signed Rank test was used when the distribution of the data was not normal. Variables related to participant characteristics and variables related to the epileptic condition were evaluated in terms of their correlation to neuropsychological performance. These variables included: disease duration, time since last seizure, age of onset, years of education, age, medication, gender for the patient group and years of education, age and gender for the control group. The Pearson correlation was used in order to evaluate the

correlations for variables with normally distributed data and the Spearman correlation coefficient was used for non-normally distributed data. Statistical significance was accepted when P<0,05.

Results

Participants

Participants in the control group and the patient group were similar in age, gender distribution, level of education and hand preference. The data are given in Table 1.

Table 1. Demographic characteristics of the patient and control groups

	CONTROL GROUP	JME GROUP
Number of Participants (N)	15	15
Gender (M/F)	4 / 11	4 / 11
Chronological age (years), Mean (standard deviation)	31.27(3.37)	31.6(3.51)
Education, primary, secondary, higher (v)	1/15, 5/15, 9/15	1/15, 5/15, 9/15

Differences between the two groups in performance on the cognitive tests

a) The two groups differed in terms of their performance on the FAB test (t(14)=2.75, P=0.016) with the control group (mean=22.4) performing better than the patient group (mean=21.2). Further analysis reveals that the significant difference is mainly because of the difference in performance on the third FAB subtest which measures motor programming (Z=-2.16, P=0.031).

b) There is also a significant difference between the two groups in their performance on the verbal fluency tests. Total fluency (t(14)=5.05, P=0.01), phonological fluency (t(14)=2.76, P=0.00) and semantic fluency (t(14)=4.68, P=0.00) all reached statistical significance in their difference on the performance of the two groups with the control group having higher performance in all three scores.

c) For the Stroop test measures no significant differences arise, with a tendency for the patient group to score lower, with the exception of the second (reading) subtest where the difference in performance reaches statistical significance (t(14)=-2.36, P=0.034) with the patients taking more time to read the words (mean=53.4 sec) than the controls (mean=45.8 sec).

d) Total IQ measured by the WAIS-III subtests of Vocabulary, Similarities, Block Design and Matrix Reasoning did not reveal a significant difference between the two groups with the control group having the tendency to score higher than the patient group. Looking at each subtest separately reveals a significant difference in performance of the two groups for the Vocabulary subtest (t(14)=2.25, P=0,04) with the control group (mean=48.7) having higher performance than the patient group (mean=43.7).

e) For all the rest of the neuropsychological measures on cognitive performance there were no significant differences for the two groups. In most measures inspection of the means reveals a slightly higher performance for the control group.

All the significant differences in cognitive performance between the two groups are summarized in Table 2.

Table 2. Significant differences in cognitive performance between the two groups.

Test	Shapiro-Wilk test (P-value)	T	Df	P-value
Vocabulary (WAIS-III)	0.87	2.25	14	0.04
Phonological Fluency	0.32	2.76	14	0.01
Semantic Fluency	0.30	4.68	14	0.000
Word Fluency (total)	0.78	5.05	14	0.000
Fab (total)	0.206	2.75	14	0.016
Reading subtest (Stroop)	0.95	-2.36	14	0.03

Relation of different variables for both groups to the neuropsychological performance.

Patient group: a) Duration of disease was correlated significantly to phonological fluency (r= - 0.569, P=0.027) and to the time taken to complete the second (reading) subtest of the Stroop test (r=0.58, P=0.024). Performance to all the tests declined as the duration of the disease increased. b) Time since the last seizure was correlated significantly with performance on the Digit Symbol test (r=0.55, P=0.03). In most tasks performance increased as time since the last seizure increased. c) Age of onset was only correlated positively to performance on Trail Making A (r=0.523, P=0.046) and there was no other correlation with performance on the rest of the tasks. d) Years of education was correlated significantly with the total IQ score (r=0.59, P=0.02), with performance on the Digit Symbol task (r=0.55, P=0.035), with performance on the Digit Span task (r=0.61, P=0.02), with performance on the

Trail Making A task (r= - 0.573, P=0.03), with performance on the third subtest of motor programming of the FAB test (r=0.59, P=0.03) and with the total errors on the third (interference) subtest of the Stroop task (r= - 0.54, P=0.04) (Table 3). e) Age is significantly correlated with both phonological fluency (r= -0.6, P=0.02) and with the time taken to complete the second (reading) subtest of the Stroop task (r=0.54, P=0.02). It is not easy to attribute this correlations to the age or the duration of the disease factor. f) ANOVA and the Kruskal-Wallis test showed that the type of medication did not have any significant effect on the neuropsychological performance. g) And finally there was no difference between the two genders on performance.

Control group: a) Years of education was correlated significantly with performance on the Digit Symbol task (r= 0.768, P=0.001) and to all the Stroop test measures with performance increasing as the years of education increased. Performance on the rest of the neuropsychological tasks did not show any significant correlation. b) Age was correlated significantly with performance on the Rey-Figure task both for immediate and delayed recall (r= -0.53, P=0.04) with performance decreasing as age increased. c) There was no difference in performance between genders.

Table 3. Significant correlations between years of education and cognitive performance for the patient group.

Patient group		
Test	Pearson's r	P-value
IQ (total)	0.59	0.02
Digit Symbol	0.55	0.04
Digit Span	0.61	0.02
Trail Making A	-0.57	0.03
FAB (motor prog. Subtest)	0.59	0.03
Stroop (total errors, 3rd t.)	-0.54	0.04

Discussion

In the present evaluation of cognitive function of JME patients previous findings of a general impairment in cognitive performance are not confirmed. Also, a specific impairment for executive functioning is not totally supported. What is found is an impairment in word fluency which is in agreement with almost all previous studies and an impairment in motor programming as it is measured by the FAB. Similar impairments to motor programming for this particular patient group are also reported by video-EEG studies that look at the provocative effects of action programming (higher mental activities requiring hand movements such as written calculation, writing and spatial construction) [31-37]. However, the number of participants in this study is not very large and studies with much bigger samples may detect cognitive impairment in a larger scale. Also, the patients that have agreed to participate may have higher cognitive functions than those that did not agree to participate, thus making the study biased to a certain extent.

Significant differences were also found in the reading subtest of the Stroop and vocabulary subtest of the IQ measurement. It is argued that these differences may be related with difficulties in word processing for the patient group, although further research is needed to verify this. Along with these significant differences between the patient and the control groups there is a general tendency for the patients to perform lower in all tests including the IQ measurements but this tendency does not reach statistical significance.

The FAB tests include a verbal fluency test in which a significant difference for the two groups is not detected as it is with the standard verbal fluency test. This is attributed to the small scoring scale used by the FAB test which probably produces a ceiling effect. The FAB takes only 10 minutes to be completed and gives an evaluation of general frontal abilities. An extension of the scoring scales for all FAB subtests may produce a good diagnostic and cognitive function evaluation tool for JME.

Cognitive impairment in verbal fluency and motor programming may be related with the thalamus and specific thalamic nuclei such as the intralaminar nuclei (ILN) of the paramedian thalamus which have been found to mediate functions such as these [39-41] and have, also, been found to be implicated in executive functions [42-46]. This proposal is in agreement with the thalamocortical network dysfunction hypothesis for JME [11, 13]. It has been found that deep brain stimulation in the thalamus may alleviate symptoms of different neurological disorders [47] and brain surgery in the thalamus may help with obsessive compulsive disorder, neurogenic pain, movement disorders and epilepsy [48, 49]. Also, thalamic function plays an important role in the neuromodulation of cortical function [50-52]. Thus, the thalamus it's function, thalamocortical circuitry and possible interventions at this level may lead to possible ways of treating JME. It is argued that cognitive interventions such as training in specific cognitive skills and maybe avoiding functions that may precipitate epileptic activity such as motor programming or verbal fluency early on in the onset of the disease and maybe even later on may alter the progression of JME and it's effects on brain function. Further research is needed to evaluate these proposals. The cognitive impairment that is detected in JME also, suggests the possible existence of learning difficulties for this patient group. An investigation on whether these patients have learning difficulties or not is needed.

In relating different parameters with cognitive performance a strong positive correlation is detected between cognitive performance and years of education for the patient group. The positive effect of education is revealed in a broad array of cognitive functions such as attention, memory, speed of processing, motor programming and even IQ measurements. This finding is in agreement with previous studies [22]. The effect of the number of years of education on the cognitive profile of patients is quite different from the same effect on healthy controls who had a significant correlation between years of education and performance mainly on the Stroop test. It may be possible that in each group the brain is organized and functions in different ways in responce to the education process. Further research is needed to detect whether this positive effect of education on cognitive function in JME may be used in helping patients to function better. However, it is not clear whether this educational effect can be attributed to the education process having a positive effect on patients brain function or to higher cognitive abilities for those patients that stay in school longer. Further research is needed to elucidate this, but it is argued that the education process probably does help to a certain extent with enhancing cognitive performance. More investigations are needed in order to conclude whether it can help JME patients and their cognitive abilities. The other parameters investigated in relation to cognitive performance in JME do not give conclusive findings. Further research is needed to explore their effect, although the findings so far have not been convincing [20, 22].

There is a number of investigations on cognitive performance in JME [12-23]. Although most studies propose an impairment in executive functioning this is not verified by a recent meta-analysis of the results so far [24]. The present study detects specific impaired domains of executive functioning rather than an extensive deficit. The impairments found can be linked to thalamocortical circuit functions. Further research on verbal fluency, motor or action programming, word processing, education and learning difficulties in JME may shed more light on the issue and provide a better evaluation of the conclusions so far. The cognitive evaluation of JME patients does seem to promise new insights on brain function, cognition and epilepsy, as well as possible ways for tackling the problems in JME using cognitive or neuropsychological interventions.

The authors declare that they have no conflicts of interest.

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Functionality in Alzheimer's disease: clinical symptoms, measures and management

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Abstract

It is widely known that functionality problems in addition to difficulties in cognition is a crucial issue for Alzheimer's Dementia. These deficits in executive functioning have been hypothesized to reflect AD pathology in prefrontal cortex. For clinicians is very important to have specific tests and scales so as to determine if the patient has AD or another type of dementia. One of these signs is the ability of livening independently. Special questionnaires and tests have been used for clinical practice. In this study we present the most widely used tests in Greece, which have shown the best validity and specificity. AD Cooperative Study-Activities of Daily Living Inventory (instrumental subset) (ADCS-iADL), Dependence Scale (DS), Disability Assessment for Dementia (DAD-ADL), FUCAS and FRSSD are the tests which are globally used for assessment of functional problems of patients with AD. We conclude that the test which has the highest specificity and must be applied from every clinician is DAD-ADL, although in clinical trials ADCS-iADL is usually used .

Introduction

There is no much known about the correlation of quality of life and functionality of people with dementia in long-term care settings, and more information is needed about the properties and the way of evaluation the quality of life aimed at this group. This paper presents the questionnaires designed to assess early functional deficits and compensatory strategy use that may mitigate functional decline that occurs in elderly with cognitive impairment.

Functional evaluation can be measured by many methods. Many scales have been applied for measuring functional impairment objectively and evaluating the efficacy of treatment in patients with AD. Several scales focus on either BADL or IADL. For assessing functionality in AD, instruments specific to dementia should be used in order to evaluate the stepwise and subtle functional decline and the response to therapy[1]. Two systematic reviews [2,3] summarized current evidence with regard to this topic. They report the presence of depressive symptoms to be most consistently related to low self-reported and low proxy-reported QoL. In addition, they found an association between behavioral disturbances, especially agitation and low self-reported QoL.

Dementia is characterized by progressive deterioration of cognitive, emotional, behavioral and functional abilities for a long period [4] and is classified into 7 stages according to the Global Deterioration Scale [5]. At stage of mild cognitive impairment (MCI), the symptoms can be recognized easily and the patient can live independently without assistance. At later stages, independent living is a big problem.

Generally, dementia affects patient's ability to function in everyday activities and to perform personal activities of daily living such as bathing, dressing, eating and preparation of meal, transferring and toileting. Thus impairment of functionality increases the risk of being admitted to nursing home care or to long-term care facilities because as increasing P-ADL impairment increases the dependency of the patient and needs 24-hour protection. Lower P-ADL functioning increases the burden for the patients, their family, the caregivers and society as a whole [6].

Questionnaires represent one of the easiest and cheapest options for administration, assessment and data gathering. They require insight and intact cognition to obtain accurate depictions of functional performance. Informant report further requires identification of individuals that spend adequate time with the patient so that they can report on daily functioning. Self-report measures have shown poor correspondence with objective measures of cognition and poor reliability in individuals who lack awareness of their deficits [7], whereas informant-report measures have routinely shown moderate correlations with objective cognitive measures [8] and the ability to differentiate between diagnostic groups [9]. Unlike data derived from performance-based measures, individuals are able to base their responses to questionnaire items on multiple observations of everyday tasks in a variety of real-world environments, taking into account compensatory strategy use and environmental supports. Although the majority of functional questionnaires provide an adequate portrayal of significant functional change that occurs with dementia, several newer scales are sensitive to more mild difficulties [10] e.g. the activities of daily living-prevention instrument, ADL-PI [11], none of these scales capture compensatory strategy use for instrumental activities of daily living (IADL). Prior research suggests that older adults with better memory skills respond to subtle memory changes by implementing more compensatory strategies than individuals with poorer memory skills [12]. A growing body of literature also suggests that individuals with MCI can learn to use both internal (e.g., mnemonics) and external (e.g., memory notebook) aids to help compensate in daily life for memory loss [13]. Given the importance that Older

Adults place on remaining in their own homes [14] and cost of nursing home care [15], understanding how individuals use compensatory strategies to assist in maintaining functional independence in their homes as cognitive changes occur is of significant value.

Subjects and methods

There are many questionnaires which assess the Activities of Daily Living. Some of them will be described in the following lines.

1. Functional Rating Scale for Symptoms of Dementia (FRSSD)

The Functional Rating Scale for Symptoms of Dementia assesses the functioning of the patient in 14 everyday life activities: food, clothing, incontinence, speech, sleeping, face recognition, personal hygiene, and memory for names, episodic memory, vigilance, global confusion, orientation (place), emotion, and social behavior. The rating scale ranges from 0 to 3 points, that is, from no impairment (0) to severe impairment (3). The FRSSD is administered to the caregiver rather than the patient him/herself. Therefore, the report may be influenced by the emotional and physical impact caused by the disease on the caregiver. A score of 5 is proposed as the cut-off point for the differentiation between healthy persons and patients with possible dementia. Tsolaki et al [16] found in their study, that the presence of extrapyramidal symptoms (EPS) imposes difficulties in daily activities, as seen by the fact that patients with EPS have higher FRSSD scores (mean ± SD: 14.87 ± 10.53) than patients without EPS (5 ± 2.58). This outcome make FRSSD test a powerful tool to determine people only with AD without EPS

2. Functional Cognitive Assessment (FUCAS)

Functional Cognitive Assessment is a 13-item scale that asks patients to execute 6 different activities of daily life. The activities include telephone communication, shopping, orientation in place, taking of medication, personal hygiene, and clothing. The examiner evaluates through constant direct observation seven parameters of executive function during the execution of each daily activity by the patient. The parameters assessed are awareness of the problem, working memory, planning of the solution, distribution of time between the steps of the activity, sequence of steps, accuracy of steps, and goal maintenance. A score of 1 indicates no problem with the executive parameter that we examine in a certain activity, 2 indicates a mild-to-moderate problem, and 3 indicates a severe problem. FUCAS is designed to provide also a sub score of performance for each executive parameter which reflects the total patient's performance in the six activities. Thus, a score of 6 indicates no problem with the executive parameter assessed totally in all the six activities, 7–12 indicates a mild-to-moderate problem, and 13–18 indicates a severe problem. It is also possible to extract a sub score of total executive function in every activity assessed. A score of 7 indicates no problem with total executive function in a certain daily activity, 8–14. Kounti et al [17] in their study examined 192 men and 256 women, 55–88 years old, in the validation study of FUCAS. The total score of FUCAS was significantly correlated with the total score of Camcog (r =0.784), MMSE (r =0.781), and FRSSD (r=0.623). Also, they found a strong correlation between the executive parameters of FUCAS and the total score of CAMCOG and MMSE. FUCAS is a reliable diagnostic tool also for MCI, because it assesses parameters of the executive function, which are responsible for IADL. Working memory, Awareness of the problem are severely impaired during the moderate-severe stage of dementia. Moreover, descriminant analysis has identified that FUCAS was able to sufficiently discriminate the patients with MCI from those with moderate to severe dementia. Working memory, Awareness of the problem were the critical parameters of executive function for this classification, because they are severely impaired during the moderate-severe stage of dementia. Impaired or spared ability for Telephone communication was also able to discriminate MCI patients. Also, FUCAS is a useful and reliable diagnostic tool for MCI, since it assesses parameters of the executive function, presumed to be mainly responsible for the impairment. We suggest that directly observed cognitively as well as behaviorally based assessment such as that provided by FUCAS can provide objective information that can serve to enhance the quality of clinical decision making.

3. AD Cooperative Study-Activities of Daily Living Inventory (instrumental subset) (ADCS-iADL)

Cooperative Study-Activities of Daily Living Inventory (instrumental subset)[ADCS-iADL]) [18]. The ADCS-iADL is an inventory developed as a questionnaire that is answered by the caregiver. The caregiver is asked whether the patient has attempted activities of daily living within the preceding 4 weeks. If the patient has done so, the caregiver is asked to rate the patient's performance level based on a set of performance descriptions. Scores range from 0 to 56, with higher scores indicating better functioning in performing activities of daily living. Ascher-Svanum, et al.[19] examined patients with dementia and diabetes and found that all of the patients with mild AD had functional decline over the follow-up period but the patients with diabetes demonstrated a significantly lesser magnitude of decline at 18 months (LSM difference on ADCS-iADL, –3.07; 95%CI, 0.62–5.53; P = 0.01). During the 18-month follow-up, the non diabetic group had a decline of 5.87 , whereas the diabetic group changed very little on the ADCS-iADL measure. The 2 sensitivity analyses provided essentially the same, significant, results. Another study [20] has proved Analysis of rivastigmine treatment effects on the ability to perform individual ADL has previously shown significant benefits of rivastigmine over placebo on several ADCSBADL and IADL domain items, including bathing, clearing dishes after a meal, obtaining a beverage, disposal of garbage, traveling outside of the home, shopping,

talking about current events, writing, and using household appliances. These results shows the sensitivity the ADCS scale has to identify improvement of people with dementia especially in clinical trials .

4. Dependence Scale (DS)

The Dependence Scale (DS) [21] is a brief instrument composed of 13 items. The scale is composed of 3 subscales, a cognitive support dimension, a dimension related to types of assistance in which the individual is active, and a dimension related to types of assistance min which the individual is completely passive. Reliability coefficient (Cronbach a) for the scale as a whole is 0.66, and coefficients for each subscale are 0.93, 0.87, and 0.87, respectively. The validity of the DS was established according to the relationship with several clinical indicators. A global dependence score is ranging from 0 to 15, with higher scores indicating greater degree of dependence and lower scores prove the deterioration of demented person. The DS has been used in several clinical trials and observational studies [22]. The DS has been shown to be significantly and independently related to measures of cognition, functionality, and behavior [23]. A recent study by McLaughlin compared different potential measures of AD severity regarding their ability to bridge between changes in AD symptoms and economic or quality-of-life outcomes showed that the DS score might be an appropriate candidate [24] In a recent study, Garre-Olmo et al [25], examined the relationships of the DS with other dependence-related measures in order to assess the concurrent criterion validity. The degree of association of the DS score with the OSADD score was appropriate. The OSADD is the tool used by the Spanish Ministry of Health, Social Policy, and Equality to determine the degree of dependence of individuals. In Spain, the official recognition of a certain degree of dependence entails the right to access to social services and economical benefits, and the OSADD score is the basis to determine the type and amount of benefits that an individual could receive [26].Completing the OSADD requires trained professionals and the mean administration time is about 30 to 40 minutes. The high correlation observed between the DS and the OSADD supports the concurrent criterion validity against a robust gold standard. The confirmation of the hypotheses related to the high correlation between the DS score and an objective measure such as the hours attending basic and instrumental ADL, and supervising the patients, also supports the robust criterion validity of the DS because dependence is defined as the level of assistance required by the patient. In this sense, the higher the number of hours needed to attend the patient, the higher the degree of dependence. Although these results are not directly comparable with those from the original study due to differences in the instruments used, our results corroborate that the DS has robust criterion validity.

5. Disability Assessment for Dementia (DAD)

The Disability Assessment for Dementia (DAD) scale [27] developed by Gelinas et al is one of the scales that evaluate the functional activity, in patients with AD. It has excellent psychometric properties either in every language version. The DAD scale gives information about the nature of the functional deficit and at which step a function is impaired. These features help physicians and caregivers in planning treatment and care and measuring the effect of therapy. In a recent study by Tozlu et al [28] DAD score showed significant differences between different stages of the disease indicates that the scale is a valid indicator of disability and can discriminate the patients at different disability levels. The DAD-ADL score can be used in the discrimination of the patients at different stages of functional disability. The DAD-IADL score can be used, especially in the discrimination of the patients at stages 4 to 6. The DAD total score was found to be moderately correlated with Lawton and Katz scales in De Vreese et al [29] study, in which only patients with very mild and mild AD had been recruited. On the other hand, the patients at mild, moderate, and severe stages of AD were included in their study. Mok et al found a strong positive correlation between IADL part of DAD scale and Lawton IADL [30]. These results also indicate that DAD scale reflects the patient's functional disability by evaluating IADL and BADL at 1 scale. The DAD total score was affected mostly by Geriatric Depression Scale (GDS) and subsequently MMSE and the duration of the disease. The finding of internal consistency coefficient Cronbach a to be above .60 showed that DAD scale measures distinct sides of functional disability. The DAD scale showed excellent test-retest and interrater reliability. These results were compatible with the scale's original article and other reliability and validity studies. These results can be interpreted as DAD scale is a reliable tool for measuring functional disability in patients with AD.

Discussion

In order to deal with the heterogeneous clinical expressions of AD between individuals, there are different strategies to adopt, with their own strengths and weaknesses. One of them is the utilization of individualized measures using goal-attainment scaling procedures [31]. This approach consists of characterizing the clinical status of the patient using distinctive qualities and particularizing the efficacy of the interventions by setting goals related to a specific patient. This approach has proved to be feasible, valid, and responsive in dementia [32] Another approach is the use of the dependence construct as the indicator of disease progression [33]. Dependence has been defined as the level of assistance required by a patient and can be characterized as the measurable impact of changes in cognition, function, and behavior that result in an increased need for assistance. The lack of a concise operational definition of the construct as well as the lack of instruments developed to assess dependence in patients with AD has limited its use as indicator of disease progression. This study was aimed to explore the psychometric attributes of a scale for cognitive and functional assessment of patients in the most advanced stages of dementia. A reliable,

valid and sensitive scale would help to cover the need of appropriate instruments for evaluation of patients in this situation, where the usual measures for less severely demented populations are not useful.
Our study as well as the results of the Swedish study indicates the importance of care for persons with dementia as the dementia disorder progress and the P-ADL decrease. We suggest that directly observed cognitively as well as behaviorally based assessment such as that provided by FUCAS can provide useful information that can serve to enhance the quality of clinical decision making. Cognitive functioning, functional rehabilitation and treatment of depressive symptoms should receive special attention.

A change in functional capacity or dependency in functionality among people with Alzheimer disease is a crucial issue nowadays and need to be recognized as the main problem of demented people. In our opinion we believe that early diagnosis of functional problems is a sign of dementia and a good instrument with high sensitivity and specificity must be applied by doctors to determine if their patient has AD. From many scientists the ADAS cog is best suited for assessing mild-to-moderate stages of dementia [34,35] due to floor effects in patients with more severe AD. Although the ADAS-cog may not have been sensitive enough to detect dose-related differences reliably as patients progressed to the later time points as it has been proved by study of Cummings et al [36]. For instance, we believe that DAD-ADL is a reliable instrument which can be used by any physician for patients with AD. On the other hand clinical and neurological examination must be applied to every patient so as to determine the right diagnosis.

Post hoc analysis of OPtimizing Transdermal Exelon In Mild-to-moderate Alzheimer's disease (OPTIMA), a double-blind trial comparing 13.3 and 9.5 mg/24 h rivastigmine patch in patients with AD demonstrating functional and cognitive decline with 9.5 mg/24 h patch. Efficacy on Alzheimer's disease Cooperative Study-instrumental ADL (ADCS-IADL) items, higher level function (HLF), and autonomy factors was assessed. The ADCS-IADL, HLF, and autonomy factors favored 13.3 mg/24 h patch at all time points, reaching significance from weeks 16 to 48, 24 to 48, and 32 to 48, respectively. Higher dose patch demonstrated significantly greater efficacy on 10 of 17 ADCS-IADL items at 1 or more time points ($P < .05$ vs 9.5 mg/24 h patch)[37].

The authors declare that they have no conflicts of interest.

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Evaluation and management of speech, language, communication and eating disorders in dementias – how this can improve clinical care? – A short review

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Abstract

The dementias represent a group of devastating, incurable, neurodegenerative diseases, affecting predominately older individuals. Among their clinical characteristics, speech, language, communication and also eating and swallowing disorders are of special interest due to their importance in diagnosing, staging, understanding the pathophysiology, but also designing and conducting therapeutical interventions. Furthermore they are the leading cause for the deterioration of the quality of life, as judged by patients, their families and caregivers, as they challenge their ability to communicate and eat. Clinicians are disappointed with the limited usefulness of the current available pharmacological interventions and the ideal situation of establishing biomarkers capable to detect pre-clinical patients and providing interventions preventing the progression of dementias is still an unmet goal. On the other hand, there is growing evidence of the importance of a multidisciplinary approach involving neurologists, clinical neuropsychologists and speech and language therapists under the umbrella of neuropsychological rehabilitation, focusing at dementias' patients and their caregivers. Such an approach is especially important for: a) offering earlier and more accurate diagnosis and classification of neurocognitive disorders b) designing and conducting therapeutic non-pharmacological interventions focusing on cognition and language which improve and maintain functional communication, and c) prolonging self-feeding period, maintaining nutrition and hydration and reducing the incidence of life-threatening complications, such as aspiration pneumonia.

Introduction

In this short review we are focusing on several issues releavant to the diagnosis and management of the various forms of dementias, especially of Alzheimer's disease (AD). Of special interest of course is the imperfect medical-pharmacological treatments, the need for multidisciplinary approaches for diagnosis, counceling and management of the complicated issues arising, and the nonpharmacological interventions. We discuss data from the recent literature, criticise some clinical trials, but also provide empirical data from our own experience treating demented patients and their families. Alzheimer's disease (AD) is the most common cause of dementia and represents one of the most unmet needs in medicine today. By 2013 affected 44.4 million people globally and is expected to affect 75.6 million by 2030. Alzheimer's Disease International estimates that the prevalence of AD will increase by 225% by 2050, affecting more than 115 million people worldwide [1].

Epidemiological projections of the prevalence of AD and related dementias, the rapidly expanding population over the age of 65, and the enormous societal consequence on health, economics, and community foretell of a looming global public health crisis [2]. Traditionally AD has been diagnosed and its course followed based on clinical observations and cognitive testing, and confirmed postmortem by demonstrating amyloid plaques and neurofibrillary tangles in the brain. But the growing recognition that the disease process is ongoing, damaging the brain long before clinical findings appear, has intensified a search for biomarkers that might allow its very early diagnosis and the objective assessment of its responses to putative treatments. At present at least eight biochemical measurements or scanning procedures are used as biomarkers, usually in panels, by neurologists and others. The biochemical measurements are principally of amyloid proteins and their A-beta precursors, or of tau proteins [3].

In 2011, more than a quarter of a century after the original diagnostic criteria for probable Alzheimer's disease were published, new diagnostic guidelines were published covering the continuum of Alzheimer's disease. There is also an encouraging progress in biomarker validation and genetics. The NIA-AA (the National Institute on Aging (NIA), part of the US National Institutes of Health, and the Alzheimer's Association (AA)) guidelines included a specific framework for biomarkers across the continuum of disease, dividing them into two categories - markers of amyloid-β accumulation and markers of neuronal injury or neurodegeneration. This division was based largely on the earlier seminal work by Jack and colleagues, describing a hypothetical temporal ordering model of biomarkers across the range of Alzheimer's disease stages [4-7]. Recently, an updated version, DSM-5, was published; key updates are the change in dementia to the newly named entity "major neurocognitive disorder (NCD)", and recognition of a less severe level of cognitive impairment, termed "mild NCD" [8].

The most recent diagnostic guidelines from the National Institute on Aging and Alzheimer's Association define three stages of AD:

- Preclinical phase: neuropathologic changes occur, no overt (or only subtle) symptoms.
- Phase of mild cognitive impairment: symptoms become apparent; activities of daily living (ADL) are preserved; the patient does not have dementia.
- Dementia phase: ADL are impaired.

However, despite diagnostic advances there has been continued disappointment in clinical trial results. Although considerable efforts have been made to develop effective therapeutic agents for AD therapy, drug development has not met significant clinical success. Current pharmacotherapy of AD is limited to cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine. Since amyloid-β(Aβ) has been implicated in AD pathogenesis, the use of β secretase inhibitors as well as immunotherapy against Aβ has been investigated, as well the therapeutic potential of antioxidants and anti-inflammatory agents in AD treatment. Despite these efforts, drug development for AD has proved extremely difficult and most clinical trials have afforded disappointing results [9-10]. Among clinical features of dementia, speech, language, communication and also eating and swallowing disorders are of special interest due to their importance in diagnosing, staging, understanding the pathophysiology, designing and conducting therapeutical interventions, but also because they are the leading cause for the deterioration of the quality of life (Qol), as judged by patients, their families and caregivers, as they challenge their ability to communicate and eat.

The concept of QoL relates to the 1947 definition of 'health' by the World Health Organization (WHO) as being a state of complete physical, mental, and social well-being [11]. In a similar fashion, Lawton characterized five domains pertaining to QoL for subjects with dementing illnesses to comprise the same areas as in people in general (cognitive functioning, ability to perform activities of daily living, being able to engage in meaningful time use, social behavior, as well as a favorable balance between positive emotion and absence of negative emotion) [12].

From the earliest disease stage, the patients' capacity for communication declines as problems develop with the use of language and all aspects of functional communication. There is a loss of the ability to communicate thoughts and needs, and it becomes increasingly difficult to interact socially and sustain personal relationships with caregivers, family, and friends. It is unsurprising that patients become frustrated at their loss of self-expression, and studies have demonstrated that impaired communication is strongly linked with the development of significant behavioral concerns. Overall, poor communication contributes to caregiver strain, and adds notably to the burden of disease [13].

Overall, patients with dementia who are characterized by a progressive cognitive decline, are at "high risk" for dehydration, malnutrition and aspiration pneumonia. The management of feeding and swallowing disorders afflicting patients with dementia of the Alzheimer type in the middle and late stages of the disease, is critical while maintaining the minimum required nutrition poses a daily challenge for clinicians and other health professionals. Approximately half of all dementia patients will be unable to feed themselves within eight years of their diagnosis. Moreover, 85 percent of dementia patients have demonstrated refusal to eat [14]. Weight loss is a frequent complication of AD and occurs in patients at all stages, even in the early stages before diagnosis is possible. Malnutrition contributes to the alteration of general health status, to the frequency and gravity of complications, especially infections, and to a faster loss of independence. With progressive dementia, patients become incompetent to make decisions. As a result, complex situations may arise in which physicians and families decide whether artificial nutrition and hydration (ANH) is likely to be beneficial for the patient [15].

One of the major issues attracting scientists' interest during the last decade, not only for the dementias, but practically for all the diseases affecting the brain, especially those with neurodegenerative nature, is the cognitive reserve hypothesis. Cognitive reserve could be described in simple words as the (limited) capacity of our brain to keep on doing the «job» despite the damage occuring due to the disease process. There is a threshold, below which abnormalities in cognition, behaviour and overall functioning become evident. Even if there is no global agreement for what exactly we define as «cognitive reserve», this hypothesis suggests that across the lifespan, higher education, regular participation in social or mentally stimulating activities, and complexity of occupation increase an individual's resistance to dementia. When combining different indicators in the analyses/definition, including education, occupation, mentally stimulating activities, and premorbid IQ, cognitive reserve has a protective effect against cognitive decline [16].

A life-course model of cognitive reserve in dementia was recently investigating by examining how school grades around age 10 years, formal educational attainment, and lifetime occupational complexity affect the risk of dementia in old age. Lowest risk was found in the group with both higher childhood school performance and high occupational complexity [17]. Among factors contributing to cognitive reserve, bilingualism holds a special position. A growing body of evidence suggests that lifelong bilingualism may delay the onset of clinical AD symptoms by several years, acting as a reserve against AD by protecting frontostriatal and frontoparietal executive control circuitry [18]. The cognitive reserve hypothesis is of particular interest in both premorbid or preclinical period (practically for everyone) and the clinical phase of neurodegenerative diseases. In healthy people mental enrichment could act prophylactically, while when the disease process is active, could be of help under the umbrella of neuropsychological rehabilitation. This aplies not only for dementia, but also for diseases with a neudodegenerative component, as multiple sclerosis [19]. Neuropsychological rehabilitation refers to a set of interventions that aim to improve a person's ability to perform cognitive tasks by retraining previously learned skills and teaching compensatory strategies [20].

For rehabilitation we mean a remediation process by which the functioning of an individual is rendered more efficient through the reduction of the damage and through the reduction of the dysfunction produced by illness or injury. This reduction can be achieved by acting directly on the patient or by acting on the patient's environment. From this point of view, the rehabilitation process is no longer confined to motor aspects but is also concerned with neuropsychological aspects. Cognitive, affective, and emotional deficits have a negative influence on the patient's ability to regain a good condition of health, an independent way of living and a good level of social integration, and all these apply emphatically to dementias. The need for rehabilitation is likely to increase in the near future, and this highlights the importance of an multidisciplinary approach involving neurologists, clinical neuropsychologists and speech-language pathologists, for desgining and conducting non-pharmacological treatments (NPTs), focusing on the special demand and needs of people

with dementia and their families-caregivers. NPTs can make both a realistic and affordable contribution. In contrast to drugs, non-pharmacological interventions are often of low cost, and the cost relates to human endeavor rather than expensive technology or medication, and might be made available cheaply in developing countries [21].

Methods

The medical treatments for dementias: where are we now?

Unfortunately, all the currently available treatments for AD are symptomatic, with modest effect sizes and limited impact on longer term disease outcomes. There have been no newly approved pharmaceutical treatments in the last decade, despite enormous efforts to develop disease-modifying treatments directed at Alzheimer's-associated pathology [22].
Purpose of this review is not to go into details in the enormous effort of the scientific community to find a medical cure for the dementias, so we will not refer to the clinical trials, which have runned and are running, investigating possible potent substunces for the medical treatment of dementias, especially concerning immuntherapies. What is, however, unfortunatelly the truth is that the current mainstream of medical treatment for dementia is running (almost ending) the second decade since the introduction of the one handful substances, still representing everything we have to fight dementias pharmacologically, despite many new therapeutic concepts and targets focusing on early-stage illness before the onset of dementia, and distinct classes of compounds which are now being tested in clinical trials. [10, 23].

Nothing really changed in the «real world» of treating patients pharmacologically during the past ten years. We still use the same substances which introduced 15 or more years ago. Three cholinesterase inhibitors (ChEIs), donepezil, galantamine, and rivastigmine are indicated for mild-to-moderate AD. All three ChEIs are approved in oral formulations; rivastigmine is the only ChEI also approved for delivery via a transdermal patch. Also the N-methyl-D-aspartate receptor antagonist memantine is indicated for moderate-to- severe AD [24-27]. All three ChEIs have demonstrated clinical benefits on cognitive function, global clinical status, and performance of activities of daily living (ADL). There are no proven clinically meaningful differences between the agents in terms of efficacy [28-29].

Cholinesterase inhibitors and memantine are able to stabilize or slow decline in cognition, function, behavior, and global change. In a very recent systematic review and meta-analysis cognitive effects were significant for all drugs, ranging from a -1.29 points mean difference (95% CI -2.30 to -0.28) in the 20 mg daily memantine trials to -3.20 points (95% CI -3.28 to -3.12) in the 32 mg daily galantamine group [30]. Efficacy and tolerability associated with ChEIs are dose dependent, so while high doses may be efficacious, adverse events (AEs) can be dose limiting. The agents have similar tolerability profiles, with nausea, vomiting, and diarrhea being the most common Aes [31-32].
In the lack of new treatments, we are witnessing an effort of using the existing ones in higher doses:

- Approval of high-dose 23 mg/day donepezil for moderate-to-severe AD was based on a randomized clinical trial that demonstrated greater cognitive efficacy versus the standard dose (10 mg/day) [33].
- The high-dose (13.3 mg/24 h) rivastigmine patch was approved for mild-to-moderate and severe AD, based on positive findings in the OPTIMA (OPtimising Transdermal Exelon In Mild-to-moderate Alzheimer's disease) and ACTION (ACTivities of daily living and cognitION) studies [34-36].
- In a similar manner memantine «high dosing remedies» appeared in the literature to be more effective than the already approved and widely used doses of 10-20mg/24. Extended-release memantine at 28mg/24h proved efficacious, safe, and well tolerated [37].

The efficacy of higher memantine dosing was challenged in more recent studies. Memantine extended release produced minor benefits on cognitive ability, and there was no difference between the treatment groups on activities of daily living. Authors concluded that there is no convincing evidence that the novel once-daily formulation of memantine represents a significant progress in the clinical management of AD that would justify additional treatment costs [38].
It is of course reasonable to try higher doses, with the assumption of superior efficacy, nevertheless it is not scientifically acceptable that, for donepezil for example, the next approved dose above 10mg/day is 23mg/day! So if a clinician wants to try 15 or 20mg/day, he/she is not liscenced by clinical trials to do so.The explanation of «jumping» from 10 to 23mg regimes of donepezil, or from 20 to 28mg of memantine must be searched into the pharmaceutical idustries and not at logical scientific reasoning.

While previous data supported that there were no significant benefits of the combination of donepezil and memantine over donepezil alone [39], other studies have indicated clinical benefits of a combination of cholinesterase inhibitors (ChEI) and memantine over ChEI monotherapy in Alzheimer's disease (AD). More spesifically, combined treatment with memantine and AChEIs proved effective in patients with AD, particularly in slowing cognitive impairment and preventing the onset of agitation and aggression in elderly AD patients [40]. The combination sounds sensible, and that applies globally in clinical medicine. Combining two agents with different mechanisms of action, may improve efficacy relative to single-agent therapy. So a systematic review and meta-analysis of randomized controlled trials based on a literature search was carried out. The objective was the development of guidelines on the question of whether combined ChEI/memantine treatment rather than ChEI alone should be used in patients with moderate to severe AD to improve global clinical impression (GCI), cognition, behaviour and activities of daily living (ADL). The quality of evidence was high for behaviour, moderate for cognitive function and GCI and low for ADL. The desirable effects of combined ChEI and memantine treatment were considered to outweigh undesirable effects. The evidence was weak for cognition, GCI and ADL [41].

The communication deficits in dementia

All dementias are characterized by progressive cognitive decline. The most catastrophic result of this decline is the alteration in communication ability of the patients, which is judged to contribute more significantly than many other factors in reducing quality of life (Qol) of patients and their families-caregivers. The impact of communication deficits in AD was recently reviewed. From the earliest disease stage, the patient's capacity for communication declines as problems

develop with the use of language and all aspects of functional communication. Patients become frustrated at their loss of self-expression, and studies have demonstrated that impaired communication is strongly linked with the development of significant behavioral concerns. Overall, poor communication contributes to caregiver strain, and adds notably to the burden of disease. The capacity to treat or slow the progression of communication deficits in AD would prolong patient independence. The use of pharmacological (anti-AD therapies) and non-pharmacological (cognitive-linguistic stimulation) treatments may be useful management methods [13].

Communication deficits, especially aphasia, is a core characteristic in dementias. These disorders are recognized as one of the strongest predictors for discriminating among dementia subtypes. Aphasia is evident across all of the dementias, and indeed is included in formal diagnostic criteria across them [42-43]. Alzheimer's first patient was also aphasic, suggesting that language impairment is a component of Alzheimer's disease (AD). Nonetheless, aphasia as a prominent feature of AD has been emphasized only recently. Despite the ubiquity of aphasia in dementia, its qualitative nature and severity vary substantially as functions of disease process and localization [44]. ICD-10, DSM-IV-TR, and the NINCDS criteria for diagnosing dementias lack specificity in discriminating among the many dementia variants. Differential diagnosis of dementias is complicated by a high degree of overlap in the initial presenting symptoms across dementia subtypes. Communication disorders seem to be among the strongest predictors for discriminating among dementia subtypes. As such, evaluation of speech and language disorders could make an important contribution to dementia diagnosis and its ongoing management.

The disorders of speech and language in Alzheimer's disease (AD),Vascular dementia(s) (VaDs), Frontotemporal dementias (FTDs), Parkinson's disease dementia (PDD), Lewy Body Disease Dementia (LBD), and Primary progressive aphasias (PPAs) are highlighted in the following paragraphs.

Language decline is apparent even in the early stage of the disease [45]. All AD patients have aphasia. Its severity correlates with increasing severity of dementia [46]. AD accelerates this decline regardless of patients' age, in respect with the decline in normal aging or in Mild Cognitive impairment [47]. The pattern of the language disorder is different in AD than in VADs [48-49], or in FTDs [50]. In a recent study, Karrasch M et al [51] showed that an incidental memory modification of the Boston Naming Test could be used in clinical settings especially to differentiate between normal aging and mild AD.Golden Z et al conducted a study to examine the differences in neuropsychological test performance between groups with Alzheimer's and vascular dementia. They showed that the two groups did differ on more basic tests and all the memory tests, but not on the more complex tests [52].

Language impairment in AD is primarily a result of decline in semantic and pragmatic levels of language processing [53]. Semantic processing involves language content, such as words and their meaning, and the associated impairments include difficulties with word finding, naming, and word comprehension, as well as semantic paraphasia (choosing incorrect words), empty speech (using ambiguous referents), inventing words, and loss of verbal fluency. Pragmatic processing goes beyond words and their meaning and concerns language adaptation to the social situation [53]. Examples of pragmatic problems are speaking too much at inappropriate times, talking too loudly, repeating ideas, and digressing from the topic. Deficits in pragmatic processing may also be influenced by other AD symptoms, such as impairments in memory and concentration, and disinhibition. However, it is thought that semantics and pragmatics are interdependent such that semantic deficits in word finding and naming may contribute to pragmatic problems in maintaining the topic of conversation or may overwhelm the cognitive ability of the patient, resulting in shouting or use of profanity [53,54].

In a longitudinal study of language decline in Alzheimer's disease and frontotemporal dementia [50], Blair et al showed that FTD-fv and PPA patients showed a faster language decline than AD patients. A general conclusion was that longitudinal language assessment provides a unique understanding of the evolution and progression of language deterioration in various dementias.

In a very recent study, memory, language, attention, executive and visuospatial functioning, and global cognition were assessed at least twice in patients with Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB), behavioural variant frontotemporal dementia (bvFTD), language variant frontotemporal dementia (lvFTD) and 112 controls, During follow-up, patients with AD declined in all cognitive domains. DLB showed decline in every cognitive domain except language and global cognition. BvFTD showed rapid decline in memory, language, attention and executive functioning, whereas visuospatial functioning remained fairly stable. LvFTD declined mostly in attention and executive functioning. VaD showed decline in attention and executive functioning. In other words, different cognitive trajectories are apparent in different types of dementia. These estimations of natural disease course have important value also for the design of clinical trials as neuropsychological measures are increasingly being used as outcome measures [55].

Vascular Dementias (VaDs) represent a heterogeneous group of dementias associated with cerebrovascular damage [56] (13). VaD can evolve due to multiple cortical or subcortical strokes, cerebral hypoxemia, aneurysm, small vessel ischemic disease and genetic cerebrovascular disease. Phenotypic heterogeneity is further increased by the fact almost half of all VaD patients have mixed vascular and Alzheimer's disease pathologies [57-59]. ICD-10 identifies the following VaD variants: 1) VaD acute onset, 2) Multi-infarct dementia, 3) Subcortical vascular dementia, 4) Mixed subcortical and cortical vascular dementia, 5) Other VaD, 6) VaD unspecified [59].

Frontotemporal dementia, (FTD) is the second most common dementia after Alzheimer's disease below the age of 65 years and it is characterized initially by progressive atrophy of regions of frontal and temporal cortex. There are at least three distinct FTD phenotypes, each having a particular distribution of cortical damage : a. Progressive Nonfluent Aphasia (PNFA), b. Semantic Dementia (SD), and c. Frontal variant FTD, (FvFTD). Progressive Nonfluent Aphasia is characterized by nonfluent speech [43], combined with agrammatism, phonemic paraphasias, and anomia, with relatively preserved episodic memory, visuospatial functioning, and temporal orientation [43,60]. PNFA reflects asymmetric damage to left posterior inferior frontal cortex, including the anterior insula, basal ganglia, left inferior and middle frontal gyri, dorsal, premotor and supplementary motor cortices [61]. The distribution of left hemisphere damage in PNFA

corresponds to that commonly seen in nonfluent stroke aphasia (e.g., Broca's Aphasia). Direct comparison between nonfluent stroke aphasia and PNFA showed that the extent of syntactic loss in production (i.e., agrammatism) was worse in the stroke aphasia group relative to PNFA [62]. In Semantic Dementia loss of meaning is a core diagnostic feature that affects both language production and comprehension. Other core features of SD include empty spontaneous speech, semantic paraphasias, and a perceptual disorder characterized by prosopagnosia and/or associative visual agnosia [43]. For a diagnosis of SD, patients must also show relatively preserved perceptual matching abilities (e.g., pure tones, pictures of different people, nonsense objects), intact single word repetition, and an ability to read aloud orthographically regular words [43]. SD patients experience profound communicative impairment. On structural imaging patients with SD show circumscribed atrophy affecting anterior, lateral, and ventral temporal lobe structures with relative sparing of the medial temporal lobe [63]. Frontal variant FTD, is characterized by decreased speech output, reduced conversational initiation, echolalia, and changes in the pragmatics of conversation. In FvFTD, cortical atrophy affects inferior, anterior regions of the frontal lobe (i.e., orbitofrontal cortex) [64,65]. Unlike PNFA and SD, individuals with FvFTD exhibit early changes in personality, organization, and attention [43, 63]. Core diagnostic criteria for FvFTD include a gradual decline in social conduct (i.e., inappropriate jokes, risk taking, hypersexuality), with loss of insight and early emotional blunting [43].

Semantic dementia is distinguishable from other presentations of FTD and AD, not only by fluent speech and impaired comprehension without loss of episodic memory, syntax, and phonology but also by empty speech with thematic perseverations, semantic paraphasias, and poor category fluency [66]. Questioning the meaning of words is an important diagnostic clue not seen in other groups, and behavior change is prevalent.

As Parkinson's disease (PD) progresses 70 to 80% of individuals convert to PD with dementia (PDD) and this conversion limits survival duration to aprox. 5 years (similar to LBD) [67,68]. Predictors of survival duration in PDD are among others fluctuating cognition, and degree of concurrent Alzheimer's disease neuropathology. Core diagnostic criteria for PDD include an established diagnosis of PD and impairment in at least two of the following four domains: 1) attention, 2) executive functioning, 3) visuospatial processing, and 4) verbal free recall. Communication deficits include impaired concept formation, perseveration, and reduced verbal fluency [67]. Reduced action word (i.e., verb) fluency predicts conversion from PD to PDD [69]. As PDD progresses, the cognitive and language deficits become more pronounced.

Lewy Body Dementia (LBD) represents a relatively new dementia classification with prevalence estimates varying from 15% to 35% of all dementia cases [68,70]. Diagnosis of LBD is based on presence of dementia as well as two of the following three features: fluctuating cognition, visual hallucinations, and movement disorder. Language disturbance in LBD is characterized by confabulation, incoherence, and perseveration during conversation, difficulty naming common objects, and a reduction in verbal fluency [71].

In 1982 Mesulam proposed the term Primary Progressive Aphasia (PPA) to describe a slowly progressive language impairment that persists for a period of at least two years without dementia [72]. Further diagnostic criteria for PPA include an insidious onset and gradual worsening of language (syntax, naming, word finding, word comprehension) in the absence of other causes of aphasia. PPA has been described as a "language-based dementia" [75] and as "slowly progressive aphasia without generalized dementia" [72] and other amnesic, personality, or dysexecutive deficits that impair activities of daily living [73,74]. PPA patients are now divided in 3 main variants based on specific speech and language features characteristic of each subtype [76]: a. nonfluent (nfvPPA), b. semantic (svPPA), and c. logopenic (lvPPA) In nonfluent variant (nfvPPA) initially almost all individuals present with increasing anomia and word finding difficulties [77-79]. In this respect patients are not much different from aphasics with AD, except they have relatively preserved memory and non-verbal cognition [80]. As the disease progresses, speech fluency decreases. Subjects experience progressive problems with sentence construction and syntax so that their speech becomes agrammatic and difficult to understand [81-83]. Agrammatism is among the core features of nfvPPA [76], and may resemble Broca's aphasia [82], is typically less severe than that seen after stroke [78,79]. Many patients with nfvPPA may be classified as having conduction aphasia characterized due to their poor repetition with intact auditory comprehension and fluent yet paraphasic speech [77].

Semantic variant PPA (svPPA) is the second most extensively described variety of progressive aphasia. This condition has been usually characterized by a progressive and multimodal loss of semantic knowledge [84,85]. Patients progressively lose the meaning of words, but are fluent and repeat well, resembling to "transcortical sensory aphasia". As the disease progresses, their speech is still considered fluent, but characterized by semantic jargon, frequently unrelated to the questions being asked or the topic discussed [66]. Severe, progressive anomia and markedly impaired comprehension of single words, with patients themselves frequently asking the meaning of words, usually nouns, are the hallmark of svPPA [50,66,74-76]. Semantic variant is strongly associated with FvFTD, and so early behavioral and personality changes are almost always seen in svPPA patients [66,74,75,86].

Logopenic variant PPA, or logopenic primary progressive aphasia (lvPPA or PPA-L) has been only recently described as a distinct form of PPA [84]. Although the speech output of both nfvPPA and lvPPA is slowed, with frequent word-finding pauses and phonemic paraphasias, patients with the logopenic type do not present with agrammatism, impaired motor control of speech, and aprosodia [76,87,88]. Given that patients typically have severe difficulty repeating sentences and longer phrases, while reproduction of short, single words remaining spared, the core impairment that underlies most language deficits in lvPPA has been suggested to be a phonological short-term memory deficit [87]. As the lvPPA progresses, problems with single-word comprehension and deficits with sentence-level grammar emerge. Patients with lvPPA frequently have episodic memory impairment [80] and poor arithmetic abilities [83], and so their clinical picture resembles AD. Behavioral abnormalities may be present, with apathy, anxiety, irritability, and agitation [86].

Anomia is a feature common to all three subtypes and is influenced by phonological processing. However, relatively little is known about the contributions of phonological mechanisms to the anomia of PPA and whether these mechanisms are differentially impaired in patients presenting with different subtypes of PPA [90]. Rogalski et al,

investigatetd the progression of language decline and cortical atrophy in subtypes of primary progressive aphasia [89]. Neuropsychological language performance patterns lost the sharp distinctions that differentiated one PPA variant from another. Peak atrophy sites spread beyond the initial distinctive locations that characterized each of the 3 subtypes and displayed a more convergent distribution encompassing all 3 major components of the language network: the inferior frontal gyrus, the temporoparietal junction, and lateral temporal cortex.

In PPA subtypes the language deficit (agrammatic, logopenic or semantic) initially arises as the only consequential impairment and remains predominant throughout most of the course of the disease, each reflecting a characteristic pattern of language impairment and corresponding anatomical distribution of cortical atrophy. Such associations between clinical features and the sites of atrophy have provided new insights into the neurology of fluency, grammar, word retrieval, and word comprehension, and have necessitated modification of concepts related to the functions of the anterior temporal lobe and Wernicke's area [91]. The underlying neuropathology of PPA is, most commonly, frontotemporal lobar degeneration in the agrammatic and semantic forms, and Alzheimer disease (AD) pathology in the logopenic form; the AD pathology often displays atypical and asymmetrical anatomical features consistent with the aphasic phenotype. A better understanding of these interactions might help us to elucidate the biology of the language network and the principles of selective vulnerability in neurodegenerative diseases [91].

Eating disorders in dementia

As we have already pointed out in introduction, patients with dementia are at "high risk" for dehydration, malnutrition and aspiration pneumonia. Moreover food and drink consumption is not only necessary for us to survive, but is also a major source of pleasure and cultural and social interaction. Therefore is not surprising that eating disorders in dementias are considered to contribute significantly in reducing quality of life (Qol), together with the communication disorders. The management of feeding and swallowing disorders afflicting patients with dementia in the middle and late stages is critical and represents a challenge for clinicians and other health professionals. Among them, speech-language pathologists have a central role. From the early stage counseling for adapting proper habits in organizing meals and combine them with social interaction, to the «to tube or not to tube» decisions at the final stages, speech-language pathologists must be considered as the protagonists. Due to the unique but also underestimated importance of eating disorders in dementias, and the key role of speech-language pathologists to them, we devote a special review on dysphagia in dementias in this issue of the Hellenic Journal of Nuclear Medicine.

Multidisciplinary approach: neurologist, clinical neuroscychologist and speech-language pathologist and the non-pharmacological treatments.

Coping with diseases, especially complex ones as dementias, could never be an «one specialty's privilege». On the contrary the duty of diagnosing, counseling and treating patients and their families must be shared among clinicians and mainly neurologists, clinical neuropsychologists and speech-language pathologists.

Neurologists are trained to investigate complex medical issues related to the nervous system with an emphasis on localizing lesions. The neurological examination must however be incorporated into the context of the patients overall health history and general physical condition. Many neurological disorders present with neurocognitive and neurobehavioural symptoms and in the case of neurodegenerative disorders (dementia syndromes) assessment of memory and other cognitive impairment is essential for diagnostic and rehabilitation purposes. Neurologists often struggle to interpret the results of neuropsychological testing, even though cognitive assessments are an integral component of the diagnostic process in dementia syndromes [92]. Although cognitive dysfunction may be suspected following a careful clinical neurological assessment, neuropsychological assessment quantifies the extent and severity of change. A good example requiring neuropsychological assessment is multiple sclerosis. Approximately half the multiple sclerosis cases assessed by clinical neurological examination did not reveal cognitive decline, as its utility in identifying cognitive deficits is low [93]. Further, the pattern of cognitive impairment in neurological disorders and especially neurodegenerative disorders may evolve over time, requiring revision of the diagnosis in individual patients. In the recently published DSM-V criteria, the diagnosis of neurocognitive disorders relies primarily on objective neuropsychological assessment, which is beyond the scope of a clinical neurological exam and requires close cooperation with a clinical neuropsychologist [94]. General cognitive screening tools, appropriate for use by general neurologists and psychiatrists, as well as specific cognitive tests examining the main cognitive domains (attention and orientation, memory, visuospatial function, language and executive function) in patients with dementia are and will be in use, but these will not replace the clinical neuropsychological assessment. We believe that clinical neuropsychological assessment will continue to be used, even in the face of advances in neuroimaging technology, because it is already well known that the presence of significant brain changes can be associated with nearly normal cognitive functioning, while individuals with no lesions detectable on imaging can have substantial cognitive and functional limitations [95]. The overall picture has of course somehow changed with the introduction of modern neuroimagining techniques, like computed tomography (CT) and magnetic resonance (MR), which allows one to determine with great accuracy the site and the size of brain lesions. In addition, the increase in average life expectancy produced a great increase in the incidence of degenerative diseases. The consequence was a great and urgent increase in the demand of neuropsychological rehabilitation. Clinical neuropsychologists are now asked to be the protagonists in designing and conducting not only assessment tools necessary to describe the pattern of deficits, helpful in defining clinical dementia phenotypes and sometimes in predicting the underlying molecular pathology, but also develop and implement therapeutic interventions [20].

As for the speech-language pathologists, they should have the central role in neuropsychological rehabilitation, in our point of view. They have to educate patients and their caregivers about the communication and eating problems associated with different stages of the dementias [96]. They also must implement direct and indirect interventions to maintain and improve the communicative and cognitive functioning of patients. In the lack of new and promising medical treatments, we think that the best we can offer to demented patients and their caregivers is the knowledge about the

gradually worsening impairments, and the tools to maintain the communicative and cognitive functioning, capitalizing the spared neuropsychological abilities to compensate for impaired ones [97]. In the following we present only a few paradigms from the data available in the literature supporting the implementation of non-pharmacological treatments in dementias.

Direct interventions are being used increasingly to maintain and improve the communicative and cognitive functioning of patients with Alzheimer's dementia. Successful direct interventions use techniques that facilitate learning and retention of information and skills. Repeated exposure via spaced retrieval training and quizzes; errorless learning; multisensory stimulation using music, toys, pets, and memory wallets; and other approaches to cognitive-linguistic stimulation such as the use of personal computers; the Montessori Method; and activity programming - are all examples of effective direct interventions. In a systematic review of the available evidence regarding cognitive stimulation, an intervention for people with dementia which offers a range of enjoyable activities providing general stimulation for thinking, concentration and memory usually in a social setting, fifteen RCTs were included in the meta-analyses for 718 participants (407 receiving cognitive stimulation, 311 in control groups). There was consistent evidence, despite the limitations of variable quality with small sample sizes, that cognitive stimulation programmes benefit cognition in people with mild to moderate dementia over and above any medication effects [98].

The evidence for clinical effectiveness and cost-effectiveness of non-pharmacological interventions for reducing agitation in dementia was systematically reviewed and synthesised in a qualitative evidence synthesis.160 out of 1916 papers screened. Person-centred care, communication skills and modified dementia care mapping (DCM), all with supervision, sensory therapy activities, and structured music therapies reduce agitation in care-home dementia residents, both immediately and up to 6 months afterwards [99].

Information and communication technologies (ICT) are potential venues for supporting the delivery of therapies that meet the social and emotional needs of people with dementia, including reminiscence therapy (RT), which is a non-pharmacological intervention involving the prompting of past memories, often with artifacts such as old photographs or music for therapeutic benefits such as the facilitation of social interactions or the increase of selfesteem. Three hundred eighty-six articles were retrieved, 44 of which met the inclusion and exclusion criteria. Findings of the systematic review include that there are benefits to using ICT for RT interventions. Some of these benefits are access to rich and engaging multimedia reminiscence materials, opportunities for people with dementia to participate in social interactions and take ownership of conversations, and a reduction of barriers due to motor deficits during interactions with media [100].

One the other hand, using indirect techniques focusing on the caregivers, so that they can learn to avoid common communication mistakes, such as correcting, reasoning with, and arguing with the person with AD. By equipping caregivers with strategies to aid verbal and nonverbal communication, clinicians can improve the interactions between patients with AD and their caregivers and lessen frustration on both sides [96]. The loss of functional communication in Alzheimer disease (AD) results from the disproportionate breakdowns in the pragmatic and semantic areas of language in these patients. A caregiver training program designed around seven specific communication strategies can be used to alter communication interactions. As a pilot program, the acronym FOCUSED organized the seven strategies for easy recall (Face-to-face, Orientation, Continuity, Unsticking, Structure, Exchanges, and Direct). Significant differences in both attitude toward AD patients, knowledge of AD, and knowledge of communication strategies were shown in comparisons of pre- and posttraining assessments [101].

Conclusions

Dementias are incurable and devastating diseases. Among their clinical characteristics, speech, language, communication and eating and swallowing disorders are of special interest and also the leading cause for deterioration of quality of life.

The scientific community is disappointed with the limited usefulness of the current available pharmacological treatments, and the lack of established biomarkers capable to detect pre-clinically patients.

There is growing evidence that an multidisciplinary approach involving neurologists, clinical neuropsychologists and speech-language pathologists is extremelly important for earlier and more accurate diagnosis and classification, understanding the pathophysiology, designing and conducting therapeutic non-pharmacological interventions direct (to patients) and indirect (to their caregivers) focusing on cognition and language, and prolonging self-feeding period, maintaining nutrition and hydration and reducing the incidence of life-threatening complications.

We cannot cure, and also we cannot prevent dementias, but what we can do as clinicians envolved in these diseases is to offer, working as a team, combinations of cost-effective pharmacological and non-pharmacological treatments able to prolong life with qood quality, maintaining the maximum degree of independence for the patients and the minimum load for caregivers.

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Evaluation and management of speech and language disorders in Alzheimer's dementia

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Abstract

Dementia impairs a person's ability to communicate effectively. Communication barriers within the person with dementia include word-finding problems, difficulties understanding information, the use of empty phrases, a lessening ability to be coherent and maintain a conversational topic. These language deficits are compounded by other dementia-related impairments including memory loss, decreased attention span, and impairments in judgement, insight, abstraction and visuospatial abilities. Speech and language therapists have an increasingly recognized and well-documented role in providing services for people with dementia. In Greece and Cyprus, there is a huge need to improve access to speech and language therapy services for people with dementia and to also develop knowledge and skills within the speech therapy profession in the care of people with dementia and their families. The benefits of providing a speech and language therapy service for people with dementia and their families according to the Royal College of Speech and Language Therapists (RCSLT) position paper on speech and language therapy provision for people with dementia (2014) rests on: (1) Providing more effective assessment through: Specific analysis of associated language disorders to inform differential diagnosis. Specialist assessment of any eating, drinking and swallowing problems. Assessment of individual's capacity to consent to treatment and care. (2) Preservation of independence by: Providing specific programs to maximize and maintain function. Enhancing function in the later stages of the condition. (3) Helping the person with dementia and those involved in their care by: Providing support that enables carers to care – support which maximizes knowledge, skill, self-efficacy and quality of life and minimizes depression and anxiety. Providing training in effective communication and management of eating and swallowing difficulties to promote good care.

Introduction

In a joint report, the World Health Organization (WHO) and Alzheimer's Disease International [1] aim to raise awareness of dementia as a public health priority; promote a public health approach and advocate for action at international and national levels based on the principles of inclusion, integration, equity and evidence for people with dementia. Our contribution is to report on the evaluation and management of speech and language disorders in Alzheimer's dementia by speech and language communication specialists working in Cyprus and Greece. It is estimated that there are currently 35.6 million persons living with dementia worldwide. This number is expected to double by 2030 and to triple by 2050 [1]. From the perspective of the two Greek-speaking countries that are the focus of this paper, the Greek Alzheimer Association reports that there are 200.000 people diagnosed with dementia in Greece (Greece has a population of around 11 million) (www.alzheimerathens.gr/) while in the Republic of Cyprus (Cyprus has a population of about 800,000) there are approximately 14,000 people living with some form of dementia of which 9,500 suffer from dementia of the Alzheimer's type (DAT) (www.alzheimer-europe.org-plans/cyprus). The word 'dementia' comes from the Latin word "demens" meaning "without a mind" and describes a collection of symptoms, that include according to the [2] definition: "a disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgment".

Dementia is *not* a normal part of ageing; the cognitive and language changes reported occur when the brain is affected by particular diseases, including Alzheimer's disease and/or the damage caused by vascular changes. Also, dementia is progressive, which means the symptoms gradually get worse with time, but how fast dementia progresses will depend on the individual person and on the type of dementia the person is afflicted with [1]. Alzheimer's Dementia (AD) is the most common type of dementia contributing to 60-70% of cases [1], and is neurodegenerative characterized by cognitive deficits, disorders of activities of daily living, language impairment and behavioral disturbances. The prominent symptoms of AD are short-term memory loss and word-finding difficulties. In addition, AD individuals have trouble with visual-spatial processing, reasoning, judgement, and insight. The part of the brain most affected is the hippocampus. Other parts of the brain that show atrophy are the temporal and parietal lobes. Nevertheless the pathophysiology of AD in the brain is very variable [3].

The need for speech-language therapy (SLT) provision

It is well documented that speech-language and communication problems occur in all forms of dementia and in the later stages of the disease, these problems become increasingly more demanding of specialist clinical services [4].

In the early stage of dementia (first two years) there is some difficulty with word-finding, while in the middle stage (years 2-5) there is increasing receptive and expressive language difficulties, and in the late stage (after 5 years) there are severe communication deficits [1].

The evaluation and management of speech-language and communication problems in people with AD poses a huge challenge for speech-language therapists (SLTs) in Cyprus and Greece with few published accounts of empirical research or empirically derived guidelines to assist with decision-making (see [5] for a first attempt). Research to guide practice is of paramount importance given the complexity of the issues related to the nature of the assessment in individuals with language and cognitive decline, and the intervention practices involved with the progression of the impairment itself. Clinical practice reveals that the assessment of acquired speech and language breakdowns in AD is a complex issue for all parties involved: SLT, person with AD, person's family, and other health-related professionals (e.g., nurse or occupational therapist) involved. This is because our understanding of basic premises underlying cognitive-linguistic deficits for Greek-speaking individuals with AD is exceptionally limited and that language abilities change dramatically with the progression of the disease.

Previous research in Greece [6] based on interviews conducted with the general public, primary caretakers, and physicians involved with Alzheimer's disease patients showed that the general public was not able to recognize the early symptoms of the disease resulting in a delay in the diagnosis. In addition, the survey indicated that only a small proportion of the physicians and the primary caretakers believed that there was an effective treatment for Alzheimer's disease but agreed on the goals of treatment. In addition there was a consensus among all respondents that the government should take a more active role as far as informing the public, supporting the caregivers, and treating the patients.

The role of the speech language therapist

Speech and language therapists (SLTs) have the specialist knowledge and skills to directly assess and manage language and communication difficulties for individuals diagnosed with AD, and any eating, drinking and swallowing difficulties as a result of dementia [7]. As communication is so fundamental, SLTs must share their clinical knowledge when participating in multidisciplinary dementia care with other team members, and propose joint goals of intervention. They also have a role in assisting other professionals to achieve effective communication with AD individuals by proposing strategies that facilitate communication and maximize positive interactions see [8].

SLTs in Greece and Cyprus work in a variety of multidisciplinary settings to contribute to the care of people with AD, including hospital words, outpatient clinics, specialist memory clinics, specialized care facilities and in the home. Unfortunately, the number of SLTs who work in adult settings is small in both countries, restricting access to speech and language therapy services for people with AD. It is crucial that policy makers and service providers address this need and ensure speech and language therapy services are adequately resourced to provide quality care for people with AD and their families.

The focus of the present review is on the role of the SLT on the evaluation and management of speech-language and communication impairment in AD. A primary role for the SLT is to assess the nature and severity of the speech/language disorder, and its impact on communication abilities. An early diagnosis of language difficulties is vital to ensure that people with AD and their families have their needs met in a timely manner. Standardized language assessments can be administered to profile speech/language skills (abilities) and difficulties with communication. Formal assessment results can be used as baseline measures to monitor the course of AD including changes to language skills and communication as a result of language and/or pharmacological interventions. There are two measures available to SLTs in Greek for diagnostic and research purposes on acquired language disorders. These are (1) the Greek version of the Boston Diagnostic Aphasia Examination [9] and (2) the Bilingual Aphasia Test (BAT) [10]. Both are described below. It is of paramount importance that the speech and language abilities of people with AD be assessed to inform two key areas: (1) that of differential diagnosis by profiling residual speech/language abilities and (2) that of intervention by documenting the needs of the person with dementia and his/her family. Furthermore, the psychological and social impact of the communication difficulty on the person with AD and their families should be acknowledged. Without the contribution of SLT specialist knowledge and skills, individuals may be misdiagnosed and appropriate treatment delayed compromising positive outcomes from specific service provisions. Finally, atypical dementias may present a particular challenge to SLTs as the presence of complex language disorder impacts on the delivery and reliability of formal language and cognitive testing (see Messinis et al., 2015 this issue).

As a final point, SLTs are uniquely qualified to assess an individual's ability to understand for the purposes of establishing mental capacity. SLTs advise on the most effective means of how to present information and choices to the individual with AD, maximizing his/her opportunity to exert free choice in decision-making ([7] p.21)

Assessment to inform differential diagnosis of language disorders in dementia

Dementia affects all aspects of communication. A number of studies in the literature have investigated the impact of different types of dementia (e.g., Alzheimer's disease, Vascular Dementia, Primary Progressive Aphasia) on cognitive-communication skills. Particular patterns of language impairment are associated with different types of dementia highlighting the important need for differential diagnosis [11]. So far, little research has been carried out on profiling the language impairment in Greek-speaking people with dementia for the purpose of differential diagnosis. In our search of the literature only one study [5] was found reporting on an in-depth assessment of the

speech/language abilities of a Greek Cypriot individual diagnosed with primary progressive aphasia (PPA), for the additional purpose of differentially diagnosing the type of PPA the person was afflicted with.

The authors compared results from the Bilingual Aphasia Test (BAT) in the three spoken languages of a multilingual male diagnosed with primary progressive aphasia (PPA). The participant was 60-years-old and showed focal atrophy of the left temporal and parietal lobes typical of PPA. He was highly educated and held a full-time job in computer maintenance. He showed relative preservation of memory and appropriate social behavior, and carried out most activities of daily living, including driving, without assistance. Prior to his illness he was highly proficient, in speaking/hearing as well as reading/writing, in Greek (both the local, sociolinguistically 'low' variety of Cypriot Greek and the 'high' Standard Modern Greek), English, and Czech. All languages were used on a daily basis for different environments (home, work, and travel). Assessment on the BAT across languages revealed difficulties with auditory comprehension for complex items, semantic interpretation, and (morpho)syntactic operations, but generally preserved repetition, reading, and writing. Moreover, he showed poor confrontation naming ability (mixed mechanism of paraphasic and word-form anomia), impaired comprehension at the sentence level, and in spontaneous speech word-retrieval deficits but preserved articulation and grammar. Kambanaros and Grohmann [5] concluded, based on the findings from the detailed language assessment, that the individual suffered from logopenic progressive aphasia (LPA). According to [12], LPA is a distinctive variant of PPA associated with a phonological (loop) disorder and with anatomic damage to the left posterior temporo-parietal regions. It remains to be seen whether Alzheimer's disease is the most common pathology underlying PPA (only after autopsy). In addition, there is long recognition that different causes of dementia lead to different patterns of cognitive decline. Neuropsychological assessment also has an important contribution to make to differential diagnosis of dementia (Messinis et al., 2015 this issue). Assessment across a range of cognitive domains (e.g., memory, executive functions, problem solving) is required to distinguish the different patterns of impairment. SLTs need to ensure that the nature and extent of the language disorder is considered when cognitive tests are administered and interpreted [7].

Describing speech and language deficits in AD for Greek

Although speech and language deficits are present in different degrees of severity during the course of the dementia disease process, the most affected linguistic areas reported in the literature to date are (a) impaired lexical-retrieval abilities (semantics); (b) disordered discourse skills/conversation (pragmatics) and (c) impoverished picture description [5-13]. With regards to speech deficits, dysarthria is the most commonly reported motor speech disorder in dementia [1]

Hardly any research is available on the linguistic abilities of Greek-speaking people with AD or other dementias. Fyndanis and colleagues [14] used a sentence completion and a sentence grammaticality judgement task to investigate subject-verb agreement, tense and aspect in ten individuals with mild AD. The results revealed that all three verbal grammatical features were impaired in individuals with dementia compared to healthy controls. In fact, aspect was more impaired than verb tense and subject-verb agreement for both production and comprehension. Furthermore, tense appeared more impaired than agreement in production. The findings revealed that morphosyntactic deficits were prominent features in the receptive and expressive language abilities of individuals with mild AD suggesting agrammatic profiles of language performance.

Kambanaros et al., [15] investigated naming of nouns and verbs using a picture-based naming task (the Greek Object and Action Test (GOAT), [16] in fifteen individuals with a diagnosis of AD, aged between 74-92 years of age compared to healthy controls matched on age, gender and education. The AD group performed significantly worse than controls on naming nouns and verbs. The difference between verb naming (68.7% correct) and noun naming (74.4% correct) in the AD group reached significance with verbs more difficult to retrieve than nouns ($z=-1.94$, $p=0.053$). This finding has been reported in the literature in AD groups for English [17-18]. The somewhat greater difficulty with verb retrieval compared to noun retrieval is attributed to the *different* cognitive demands required to retrieve verb meanings compared to nouns. No research has been conducted on motor speech disorders for Greek-speaking people with dementia.

Greek language assessment tools

The following measures can be administered by SLTs to profile language abilities and difficulties in Greek-speaking individuals with AD for diagnostic and research purposes.

1 The Greek-version of the Boston Diagnostic Aphasia Examination-Short Form [9]

A comprehensive description of this measure is beyond the scope of this paper, for details regarding the adaptation of this measure in Greece see (Messinis et al., 2013).

2. The Bilingual Aphasia Test [10]

The Greek version of the BAT can be downloaded from the official website (http://www.mcgill.ca/linguistics/research/bat). The Greek language-specific test serves as a quantitative assessment by providing numerical scores for each subtest (32 tasks), and on the BAT as a whole. Results can be grouped in accordance with the following four aspects:

- modality (auditory, visual, cross-modal)
- level of linguistic structure (phonology, morphology, syntax, lexicon, semantics)
- linguistic skill (comprehension, repetition, expression, judgment, reading, writing)
- scope (word, sentence, paragraph)

Speech and language intervention for people with dementia

The recent advances in the area of the plasticity of the brain on acquired brain injury [19] as well as its ability for adaptation to the changes due to the presence of the neurodegenerative disease in the early stages of AD [20] offer a window for intervention.

Another key factor in intervention to people with dementia (PWD), especially in AD, is that the disease does not affect equally all the types of memory. The non-declarative memory skills are preserved and can be used in intervention [21, 22].

The goals that an intervention program must have, in order to improve the cognitive-communicative skills in PWD [22] are:

a) To improve the diminished cognitive skills using the appropriate cognitive strategies.
b) To reduce demands on impaired cognitive skills (e.g., *working memory, episodic memory*).
c) To use the spared cognitive skills (e.g., *non-declarative memory systems*).

There is accumulating evidence that PWD can benefit from intervention for cognitive-communication disorders [23, 24]. A number of evidence-based intervention techniques have emerged during the last two decades as a part of the no-pharmacological therapy in PWD [22, 25-26]. The intervention techniques in PWD may be broadly divided into direct intervention strategies [27] and indirect intervention strategies [28].

The direct intervention strategies have the goal to enable the PWD to learn and retain new information and skills relaying on the spared cognitive skills [27]. On the other hand the indirect interventions have the goal to maximize the functioning of PWD. It includes the training of caregivers on communication strategies and modification of the physical environment [28].

Direct Intervention

Two of the most frequently used direct strategies in rehabilitation of cognitive-linguistic deficits in PWD are:
a) The Spaced Retrieval Training (SRT) [29-30].
b) The external memory aids [31-32].

Spaced Retrieval Training

The SRT is a technique that the PWD is required to retrieve successfully the target stimulus over progressively longer time intervals [33]. It is considered an error-minimization technique so that the response produced is correct every time [34]. This technique is based on the principle of repetition priming [29]. It has been used in a number of different training tasks in published research such as to remember a) facts (names of people and objects, current year, city and facility of residence, room number); b) to perform different procedures (how to get out of a chair, swallowing techniques); c) complete prospective memory tasks (remembering future appointments, activities, or tasks, such as looking at a calendar, taking medication); d) episodic memory tasks (i.e., remembering one's birthday, a dinner party) [35].

External Memory Aids

The use of memory aids as an external cue is a common intervention strategy in dementia care. A type of the external aids is the memory books [31-32]. Providing the appropriate system of external cues in combination with training procedure contribute to maintenance of functional memory skills of the PWD [31]. It is worth reporting that even the persons with severe dementia can be trained to successfully use memory books in everyday communication [36]. The combination of the use of memory aids with an appropriate trained caregiver can improve the communication skills of PWD [37].

Indirect Strategies

A very common indirect intervention is the use of communication strategies by caregivers of PWD in order to improve the communication interactions of PWD [38-39]. Also a number of researchers have evaluated the clinical effectiveness of structured communication training programs. Ripich [40] designed the F.O.C.U.S.E.D communication skills program in order to train nurses to communicate more efficiently with PWD. This is a structured program that includes a number of strategies for maxim communication (i.e., maintain the eye contact, keep the sentences short and direct etc). Small and colleagues [38-29] examined the effectiveness of a number of communication strategies that are indented to improve the communication with PWD. The strategies that improved the communication in their sample were: a) eliminating the distractions in the environment; b) speaking in simple sentences, and c) using yes/no questions. According to Academy of Neurologic Communication Disorders the education of caregivers on communication strategies improves the successful conversational exchanges between the caregiver and the PWD as well as help the PWD to maintain their language abilities [41].

Efficacy Data

There is an increased interest in published literature about the efficacy of the different intervention strategies in dementia's care. Recently, Hopper and colleagues [23] in a systematic review of the relevant literature supported that the PWD are capable of learning facts and procedures with the use of specific training strategies in therapy. According to the literature the severity of dementia is a key factor in effectiveness of these strategies. Persons with mild to moderate dementia seem to benefit most from the use of these specific strategies.

Conclusion, remarks and future prospects

SLTs have a professional obligation to promote the importance of effective communication for people with dementia and their families. In early dementia, communication and memory therapy can maximise and maintain communication skills and independence for longer [4].

For Cyprus and Greece it is crucial that services be made available to people with dementia and their families as soon as possible. In the early stages, there is good evidence that some areas of cognition may be relatively spared and some individuals may be able to be rehabilitated by re-learning skills to increase communicative effectiveness, and therefore reduce dependence [42] thus highlighting the need to develop appropriate care pathways and promote best practice in service provision [7]. The problems people with AD face in Greece and Cyprus include delays in diagnosis, poor integration of the different agencies providing care, unavailability of specialist services (e.g., SLT), lack of communication networks (including, people and places) to maximize communication opportunities (see 43]) and a poor understanding of the AD disease process [6]. Moreover, there is no research on the needs of the families, on how they cope with communication breakdown in the home as a result of having a family member with AD (see [44]). The RCSLT position paper rightly suggests that given people with dementia and their caregivers often have unique insights to their condition and life, they should be involved in formulating the policies, plans, laws and services that relate to them ([7]).

More research needs to be conducted on Greek-speakers with AD to document speech and language characteristics from onset to later stages of the disease along the lines of recent work on demographic and clinical characteristics of patients with dementia in Greece (see [45]). Appropriate assessment measures need to be developed for screening (see [46] on a 7-minute screening battery for AD) and diagnostic purposes that tap into specific linguistic features that are known to be problematic in AD (e.g., morphosyntax). Addressing one aspect of this paper, the inter-relationship between SLTs and policy-makers (with a clear implication for individuals with AD and their families), is underpinned by two main issues. One concerns the evaluation and diagnosis, to be then followed up by appropriate professional treatment, (i.e. speech and language therapy); the other relates to prevalence figures, that is, how common a particular communication disorder is. We briefly address both, also in line with the suggestion to policy-makers.

Identification of individuals with AD with speech/language impairments: to develop and use culture- and language-specific assessment tools for screening purposes as well as diagnostic evaluations. Also to develop on-going cognitive-linguistic assessments to further investigate linguistic differences in languages, cognitive and social factors.

Reporting prevalence of AD and communication and/or swallowing impairments: this is an important question to individuals with AD, families, professionals, policymakers, and researchers.

Importance of prevalence for service provision and funding: these are key starting points for other important enquiries. In addition to this, lifespan prevalence data are valuable in understanding the natural history, course, and prognosis of AD. Other important issues would be the assessment of possible risk and protective factors as well as the effectiveness of services. What is very surprising is the absence of prevalence figures for people with dementia who speak more than one language (are bilingual or multilingual). This is in stark contrast to the fact that more than half of the world's adult population speaks at least one language in addition to their native language [44]. This is certainly the case in both Cyprus and Greece with very large immigrant communities who speak the national language (Greek) and a minority or heritage language [5]. Research identifying modifiable risk factors of dementia is in its infancy. In the meantime, primary prevention should focus on targets identified by current evidence. These include countering risk factors for vascular disease, including diabetes, midlife hypertension, midlife obesity, smoking, and physical inactivity. One first attempt in this direction is the HELIAD study [48] that supports the important role of the Mediterranean-type diet (MeDi) in reducing the risk for age-related diseases such as AD. In fact, the study provides important data for expanding our knowledge regarding the prevalence, incidence and risk factors of AD and several other neuropsychiatric diseases in the Mediterranean.

To conclude, there is no doubt that the time to act for Greece and Cyprus is now by enforcing priorities set out in the [1] report such as promoting a dementia friendly society; making dementia a national public health priority; improving public and professional attitudes to, and understanding of, dementia; investing in health and social systems to improve care and services for people with dementia and their families; and increasing the priority given to dementia in public health research budgets by investing in high quality evidence-based research from multidisciplinary teams of researchers.

The authors declare that they have no conflicts of interest.

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Clinical presentation of dysphagia in the varied forms of dementia: A literature review

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Abstract

Objective: We sought to review the feeding and swallowing difficulties as they present in various types of dementia. When present, dysphagia poses great concern as it can lead to malnutrition, dehydration, weight loss, functional decline, aspiration pneumonia and decrease in quality of life. While it typically develops in the late stages of frontotemporal dementia (FTDA) and other dementias, signsof dysphagia can be noted during the early stages of Alzheimer's dementia. Instrumental studies have related a more sensory aspect toAlzheimer's Dementia, leading to delayed oral transit time in these patients, and have highlighted a more motor aspect in Vascular Dementia (VaD), leading to deficits in bolus formation and mastication. Recent studies revealed an increased bolus leakage time in the pharynx prior to the initiation of swallow in patients with FTD, which can explain the high incidence of silent aspiration pneumonia and its association with mortality in this population. Few studies have attempted to define the changes in food preferences, appetite and eating behaviours in patients with variants of FTD and compare them with other types of dementias. **Conclusions:** Dysphagia appears to be a common comorbid condition in patients with dementia. The onset of dysphagia as well as the mechanism causing it differs with each type of dementia. Proper identification and management of oropharyngeal dysphagia urges for a multidisciplinary evidence-based approach so thatpatients with dementia are able to self-feed longer and maintain weight and hydration over an extended period.

Introduction

Dementia is an umbrella term used for a heterogeneous group of neurodegenerative diseases defined by gradual functional and mental decline [1]. The majortypes of dementia include Alzheimer's Dementia (AD), Frontotemporal Dementia (FTD), Lewy Body Dementia (DLB), Vascular Dementia (VaD) and Parkinson's Disease Dementia (PDD).

Throughout the world, there is an estimated increase in the prevalence of neurodegenerative diseasessuch as Alzheimer's and other forms of dementia, rapidly affectingsociety's layout. It has been estimated that up to 36 million people worldwide suffer from dementia, yet prevalence figures are set to rise steeply as the number of individuals affected will double every 20 years and is projected that by the middle of the century, up to 115.4 million people will have dementia [2,3]! The recent staggeringrise in the incidence of AD and other dementias(which may approach 47% in the elderly population) is oftenattributed to the growth of the aging population (i.e. people over 60 years of age) [4]. The National Institute on Aging predictsthat, unless the disease is preventedor cured in some way, the already increased number of people suffering from dementia will be considerably aggravated, charging significantly with billions of dollars per year the total healthcare budget [5].

The most distinguishing symptoms in one type of dementia may afflict to a lesser extent individuals suffering from another type of dementia [6]. Apart from the deficits identified in language processing, behavior, memory status and executive functioning ability[7], patients with dementia slowly develop difficulties inboth eating and swallowing, for which the term "dysphagia" is used. Dementia's direct association with dysphagia,seemsto be the result of age-related changes in sensory and motor function in addition to those produced by neuropathology [8]. The immediate and proper management of dysphagia in individuals with dementia poses a growing concern, as it can possibly lead to malnutrition, dehydration, fear or even refusal of feeds, weight loss and low quality of life [9].

Despite the numerous published reports on cognitive and behavioral changes in patients with Alzheimer's disease, there are only a few studies evaluating these featuresin other types of dementia. Even more limited evidence exists regarding the non-cognitive deficits which are observed in different forms of dementia. This reviewaims to present the most recent published data on the different swallowing impairments in the majortypes of dementia.

Incidence and Prevalence of Dysphagia in Dementia

Dysphagia is a common clinical consequence of stroke and the neurologic diseases that produce dementia [8].The prevalence of dysphagia actually varies among the varioustypes of dementia and can rangefrom 13 to 57%. However, a plethora of studies report higher incidence and prevalence of dysphagia in institutionalized patients [8, 9].In the nursing home population, dysphagia has been empirically recorded up to 53%[10-12],while the percentage of silent aspirationreaches up to 68% [13].

Alterations in Eating Habits

Changes in the eating habits of patients with dementia have been established in the literatureand there seems to exist some common features among the different types.These include both increased and decreased food intake by mouth either with or without noted weight loss, new gustatory preferenceswhich involve most commonly a predilection towardssweet foods, consumption of inedible substances as well as other deficits in the typical feeding process such as the inappropriate or nouse of kitchen utensils[14].

Cullen and colleagues conducteda prospective cohort studyin which 124 patients with dementia were enrolled, 88 of which were probably diagnosed with AD disease, 20 had developed vascular dementia, 12 were suffering from Lewy body dementia and 4 of them had a form of dementia that had not been classified until the time of the study. The researchers found that the strong preference for'tasty' food was most strongly associated with Alzheimer's disease compared to vascular dementia, whilst the symptom of increased food consumption displayed heterogeneity among the different types of dementia. Interestingly enough, both aforementioned features did not display any obvious significant correlation with the severity of cognitive deficits. On the contrary, lack of appetite was considerably associated with milder cognitive impairment, probably indicating some reference to increased level of depression that may lead to anorexic behavior[15]. The correlation between the 'craving' for sweets and Alzheimer's disease is also confirmed by Trinkle's, Burn's and Levy's hypothesis that these altered food choices might be related to lesions in the central or medial hypothalamic region[16].

Dysphagia in Alzheimer's disease

The nutritional problems observed in dementia, especially in the Alzheimer's type, are worrying and have well been documented in the literature before[17].However, despite the fact that the problems around eating and swallowing are noticeable in the later stages of Alzheimer's' dementia, it is striking that we are barely informed about the precise onset of dysphagia's occurrence and its developing profile in the milder stages of this particular type of dementia [9, 18].Moreover, the way in which the disturbed physiology of swallowing interacts with attention and memory deficits, as well as with progressive aphasia,agnosia and apraxia[18], is not well understood, however, one cannot doubt its contribution to disordered ingestion of food *per os*.

Priefer and Robbins carried out one of the first studies on the evaluation of self-feeding and swallowing ability in patients with mild AD, byanalyzing videotaped dinners that the patients had along with another partner. The frequency of verbal and non-verbal cues was recorded and it was found to reach considerably higher levels in patients with AD than in the healthy age-matched control group[19]. Furthermore, individuals with AD were imitating more often their partners' acts in relation to food preparation, such as spreading butter on a piece of bread. Therefore, it becomes obvious that in the earlier stages of Alzheimer's disease, all the activities that depend on more conscious processing are disturbed in comparison to automatic movements such as bringing the fork to the mouth, which typicallyis witnessed to 'fade away' in later stages of the disease [18, 19].These researchers further evaluated patients' swallowing with a videofluoroscopicswallowing study (VFSS) and revealed considerably prolonged oral stages in these patients. Delays were noted throughout the oral transit processwith solid boluses andin the pharyngeal response time(longer time to elicit a pharyngeal swallow) as well asin the total swallowing duration with liquid boluses.These findings were of great significance as they constituted the first attempt to describe the changes in eating and swallowing process in the initial stages of the disease.

In their later pilot study, Daniels and colleaguesevaluated the effect of using verbalcues while swallowing liquids and the optimal method of liquid consumption (that provided by a clinician or by a cup), in patientswithearly Alzheimer's disease and in healthy control subjects matched by age. This study revealed that the group of AD patients eliciteda significantly more rapid bolus transit across the pharynx and a quicker triggering of the pharyngealswallow response when they were at the same time cued to swallow verbally. In both groups, the total oral transit time was considerablygreater in those trials that were administered by the clinician as opposed to those induced by the patient himself/herself (self-administered)[20].

Two recent studies published evidence of the neuronal activity during deglutition in patients with mild Alzheimer's and compared them to that of healthy subjects. The group of patients with Alzheimer's disease had significantly decreased hyolaryngeal elevation in comparison to the subjects enrolled in the control group, further substantiating the increased risk of aspiration as the disease progresses [21].Supplementary findings of this particular survey were indicative of limited cerebral activation of the cortical areas which are responsible for swallowing in the AD group. Humbert and colleagueslater studied the neuronal activity while inhibiting the swallowing process after giving the instruction "do not swallow"(an intentional 'off-state') to the patient with AD. They reported greater activation on the left anterior insula in comparison to that observed in the control group [22].The role of this particular cerebral area in both programming and initiating the swallowing process has been recognized as well by previous studies [23-25].Respectively, clinical studies have associatedlesions on the left anterior insular cortex with a delayed triggering of pharyngeal swallowing [26].Humbert et al.concluded that people suffering from Alzheimer's disease made a much greater effort to inhibit swallowing on the insular cortex [22]. Given that atrophy of the insular cortex is noted early in the disease, one can hypothesize that dysfunctions in motor planning will increase as the disease advances.

Significant findings also surfaced from Wada and colleagues' study, which proved that the average time of elicitation of swallowing reflex in patients with severe AD, is considerably longer in comparison to that which is observed in the initial stages of the disease. These researchersrevealed that the average time of triggering the

pharyngeal response after the use of neuroleptic medicationwas considerablylonger, with regards to the time reported before and after benzodiazepine consumption in this particular patient population[27].

Dementia's impact on patients' daily nutrition and hydration is changing during the course of the disease [28] and the estimated risk of aspiration episodes also dramatically increases. Horner et al.elaborated on the findings of thevideofluoroscopic studyfor 25 patients withmoderate or severe AD andnoted amarkedlyhigher prevalence of dysphagia in individuals with greater cognitive impairment. Aspiration was witnessed in 6 out of 25 (28.6 %) patientswhile only 4 patients (16%) showed swallowing within normal limits[10].The authors concluded that swallowing disorders had a direct association to dementia's duration, the level of independence in feedingand the individual's voluntary ability for oralpraxis.

Aspiration Pneumonia in Alzheimer'sDementia

Aspiration pneumonia constitutes a leading cause of death in vulnerable patient groups such as the elderly population with AD [29] and it is typically acquired while the patient is in the hospital[30]. Although more than half of the patients with dementia in nursing homesdevelop oropharyngeal dysphagia with aspiration[31], itsadverse consequences which includerecurrent aspiration pneumonia and even the risk of death, remaingenerally underrated in this patient population[32].

In their study, Wada and colleaguesrevealed the necessity of 'foreseeing'incidents of aspiration pneumonia, suggesting the consumption of the minimumeffective dosage of neuroleptic treatment, especially in the group of patients diagnosed with a severe type of AD [27]. In particular, during theirsurvey for identifying therisk factors associated with aspiration pneumonia in AD dementia, theyconcluded that aspiration pneumonia in ambulatory patients with AD, was strongly and independently associated with severe dementia, the presence of silent brain infarction (SBI) in the basal ganglia, the consumption of neuroleptic medication and male gender [27,33].

What also seemsinteresting is the varied pneumonia bacteriology witnessed in nursing homes, in comparison to that which is observed in the community. Incommunity-dwellers, *Streptococcus pneumoniae*and *Heamophilusinfluenze* typically predominate, whilst pneumonia in the nursing home or hospital setting, is most commonly attributed to*Klebsiellaspp* and *Staphylococcus aureus* colonization [34].

Dysphagia in Vascular Dementia

The study of Suh and her colleagues(2009) appears as one of the first attempts to differentiate the swallowing profile in the two most frequent types of dementia. Researchers elaborated on the findings of videofluoroscopic swallowing studies conducted with both patients with vascular dementia and patients with AD and revealed two different types of swallowing patterns. Patients suffering from AD displayedsignificantly delayed oraltransit with liquid boluses(over 5''), while patients with vascular dementia showed greater difficulties in the formation and mastication of semisolid boluses, in hyolaryngeal excursion as well as in epiglotticinversion. Patients with vascular dementia showedhigher frequency of silent aspiration[35].The authors came to the assumption that swallowing disorders in the AD patient group may arise from sensory disorders in the temporal and parietal areas, whereas the swallowing deficits seen in the group of patients with vascular dementia are probably due to motor dysfunctions in the corticobulbar tract.

Dysphagia in Frontal and Temporal Lobe Dementia (FTDA)

Swallowing disorders typically develop in the more advanced stages of this type of dementia but have not been described in detail as other behaviors have such as the compulsiveconsumption of large amounts of food. In Langmore's andcolleagues' study (2007), a total of 21 patients diagnosed with the three different variants of FTDA, namely 9 patients with FTD dementia, 7 with primary progressive aphasia (PPA)and 5 with semantic dementia underwent afiberoptic endoscopic evaluation of swallowing (FEES), in order to safely record their ability to manage solids and liquids [36].All patients with the frontal variant of this dementia, the majority of those with semantic dementia and those with primary progressive aphasia reportedchanges in theireatingpatterns. However, interestingly enough, the caregivers were far more likely to report these alterations in daily feeding routine than the patients themselves who for the most part, had no complaints. Patients in the three subtypes depicted similar eating profilesand a strong tendency to consume large amounts of foodrapidly and compulsively. Patients with primary progressive aphasia did not mention any special rituals in the feeding process in contrast with the other two groups with FTDA (for example, the need to have foods placed in a specific order on the plate).

Instrumental evaluation of swallowing revealed moderate abnormalities in swallowing inmore than half of the patients. Researchers highlighted two deviant swallowing behaviors: Firstly, the patients seemed to let the food leak intothe pharynx for a long time (up to 45'') before the actual initiation of swallow while they continued talking and chewing, showing practically no awareness that the pharyngeal area was filling up with food. The bolus was 'dumped' into the pharynx, usually reaching the valleculae, and in some cases it even fell down to the pyriform sinuses before the onset of the pharyngeal swallow. Moreover,residuein the pharynx after swallowing was observed in a high proportion of patients with FTDA, referring to limited muscle contraction that effectively drives food towards the upper segment of the esophagus (PE segment). These abnormalities could not be explained according to aberrant eating behaviors, but seemed to reflect lesions in cortical and subcortical tracts, which are mediated by swallowing centers in the brainstem.

Respectively, a recent retrospective review study in which 96 patients were enrolled, found a significant early rate of fatality in patients with FTD until the time of diagnosis[37].Patients with difficulties such asmutism or dysphagia which preceded the 'formal' diagnosis, had shorter survival, leading the researchers to the assumption that the early development of neurological deficits indicates a more insidious nature of the disorder involving more extensive degeneration of cortical and subcortical structures.

Miller and colleagues' study constituted one of the first attempts to define the different eating behaviors in patients with FTDA and Alzheimer's Disease. They found that patients with FTDA showedhypoperfusion in the frontotemporal area unlikepatients with AD who displayed hypoperfusionin the posterior temporoparietal regions[38]. With regards to the parameters evaluated, their results revealed weight gain that reached 64% in the FTDA group compared to 7% in the AD group, a strong desire for carbohydrates in 79% of patients with FTDA in contrast to 0% in patients with AD and compulsive, rapid, 'hyperphagic'(overeating) behaviors in 64% of patients with FTDA versus 14% in patients with AD. The researchers further highlighted the alterations in eating habits such as the aberrant compulsions and hyposexuality, as the initial symptoms appearing in FTDA. They concluded that the cause of these symptoms may be attributed to frontal and subcortical loss of serotonin, as well as to malfunction of the frontal temporal lobes.

Ikeda and colleaguesattempted to further differentiate the frequency of changes in eating behaviorsin the different variants of FTDA and compare them with those of patients suffering from AD, by recording changes in appetite and satiety level, food preferences and habits among other behaviors. Researchers found more changes in the eating behaviors in patients diagnosed with the frontal variant of FTD and semantic dementia, in comparison to patients diagnosed with AD [37]. They even noted some changes within the different variants of frontotemporal dementia in terms of the actual sequence of altered eating behaviors using a caregiver questionnaire.

In the majority of patients with semantic dementia, frequent changes in food preferences were initially observed, such as a marked preference for sweet tastes (seen in 80%), followed by an appetite increase and dysfunctional eating habits (stereotypic behaviors with regards to the time of daily meal consumption for example), as well as other atypicaloral behaviors (a tendency to have the mouth overfilled without masticating), while actual impairments in swallowing were observed last. In the frontal variant of frontotemporal dementia, changes in eating habits (the prolongation of a meal for example) or anincreased appetitethat involved a new cravingfor sweet tastes (seen in 91%) were among the first symptoms. In the group of patients with AD, the pattern of change was not clear andonly 21% of the patients displayed specific food preferences, yet, swallowing dysfunction (incidents of coughing and choking, delayed elicitation of swallowing) were apparent at an earlier stage of the disease. On the contrary, dysphagia with a more pharyngeal stage component seemed to develop in the later stages of frontotemporal dementia, regardless of the variant inspected [37].

Interesting results were also revealed recently by Shinagawa et al. who investigated the eating disorders in frontotemporal degeneration and highlighted the role of national and cultural factors in the daily nutrition of patients with dementia residing in both eastern and western countries[39].Researchers found that people in the United Kingdom consume significantly greater amounts of candies and their total daily calorific intake is higher than that of Japanese patients. They drew the conclusion that the altered eating behavior of people with FTDA in the western countries is not exclusively a pathological phenomenon that comes as a byproduct of the disease progression.

Dysphagia in Lewy Body Dementia

Lewy body dementia represents 15-20% of all the dementiacases based on clinic neuropathological data while the dementia associated with Parkinson's disease constitutes 3-4% [40, 41]. Recently published data of these two types of dementia in the state of Minnesota, which resulted from careful inspection of medical records of the last 15 years,revealed higher incidenceof Lewy body dementia, sharp increase with age, and greater impact on men rather than women. In fact, patients with Lewy body dementia were younger when the first symptoms developed, displayeddelusions and greater variation on the mental state when compared to patients with Parkinson's disease dementia [42].

Londos and his colleagues observed 82 patients withLewy body or Parkinson's disease dementia in an attempt to define the profile of impairedswallowing. The patients were initially askedabout their dysphagia symptoms by completing a questionnaire, and those who reported complaints, were referred for a videofluoroscopic swallowing study.In particular, 26 (32%) patients reported occasions of choking and difficulties in swallowing. 92% out of them displayed actual pathological findingsin the instrumental evaluation of swallowing and a high proportion of them (88%) depicted apharyngeal stage disorder [43]. The authors concluded that almost all the patients withLewy body dementiaor Parkinson's disease dementia who reported subjective dysphagia symptoms, did in fact revealpathological findings in the VFSS examination, most of which were of pharyngeal type. This was proved to be of significance as it had not been discovered until todaywith regards to this particular type of dementia. These results also highlight the importance of further examining the swallowing mechanism, in order to avoid the adverse complications of bolus aspiration.

Respectively, in their recent research, Shinagawa and their colleagues compared the answers of 29 patients with Lewy body dementia with those of 33 patients with AD, using a questionnaire comprised of 40items. Patients with Lewy body dementia reported difficulty in swallowing liquids and solids, coughing or choking when swallowing, prolonged swallowing time, difficulty managing sputum, decreased appetite. They also noted a heightened dependence on feeding (a need for supervision or help when eating) as well as constipation when compared to patients with Alzeihmer[44].

Weight Loss and Body Mass Index (BMI) in Dementia

A plethora of studies prove that the majority of patients with dementia lose weight as the disease advances and have lower body mass index than people with normal mental state [45-47]. In the 'spotlight' seem to be individuals suffering from Alzheimer's disease dementia as they have greater and more frequent weight loss in comparison to patients with vascular dementia[46]. Approximately 30% to 40% of patients with mild or moderate AD dementia lose at least 4% of their weight in a year [47], while around 50% of individuals in nursing homes suffer from protein malnutrition[48]. The presumable diagnosis of Alzheimer's disease indicates that the low body mass index and the weight loss constitute predictive signs of morbidity, mortality and exacerbation of the disease.

Although nutritional parameters and weight loss have been studied extensively in Alzheimer's disease dementia, patients with other types of dementia, such asLewy body dementia may be more vulnerable for malnutrition due to their eating and swallowing difficulties [49]. Faxen-Irving and colleagues found that the Body Mass Index (BMI) differed considerably by gender in various dementia disorders and was also significantly correlated with cognitive status and age.Patients with BMI<22 had more severe cognitive deficitwhen compared to those with a BMI within a normal range and overweight people[50].

The average BMI in vascular dementia and FTD was considerably higher in comparison to other forms of dementia. This difference could be attributed to changes in theeating habitsin FTDA, where 'hyperphagia' stands out as a major feature, whereas for those with vascular dementia, the highest BMI could be attributed to being overweight or to a state of obesity, both of which do, in fact, increase the riskof vascular incidents. BMI diminishes with age and it can be considered part of the normal aging process. The fact that almost 1/3 of 12.015 patients whoparticipated in the study had a BMI that indicates a risk for malnutrition, highlights the need for early nutritional evaluation and management, especially at the time of diagnosis [51, 52].

Conclusions

Dysphagia is a common condition in patients with dementia across all types and can be a result of behavioral, sensoryand/or motor problems.When present, dysphagia can complicate the course of illness as it forms a barrier to safe and adequate food intake and can lead to weight loss, malnutrition, dehydration and aspiration pneumonia. The actual timing of development of eating and swallowing problems as well as the mechanisms causing dysphagia in each dementia type,differ.The majority of studies in dementia have evaluated the cognitive deficits and little attention has been paid inexamining other non-cognitive features of the syndrome such as the changes in behavior and eating habits. As opposed to the memory decline alone, these alterations, however,are of great significance as they can potentially lead to institutionalized care.

Respectively, research has primarily focused on the late stages of AD despite the fact that changes begin earlier in the disease process. Therefore, the need of filling in the bibliographical gaps is urgentso that we can be able to identify individuals with disturbed eating and swallowing earlier in the course of the disease. This would allow for the provision of the most evidence-based practices but also would potentially prevent the adverse direct ill-effects on the patient's general health and would hopefully reduce the caregiver burden.What is todayclear from a vast empirical body of data, is that the widespread use of percutaneous endoscopic gastronomy in advanced dementia does not benefit the lifespan of these people as it was once believed.

The authors declare that they have no conflicts of interest

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Neuropsychological assessment in mild cognitive impairment and Alzheimer's disease: an overview

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Abstract

Neuropsychological assessment has featured prominently over the past 30 years in the characterization of dementia associated with Alzheimer disease (AD). Clinical neuropsychological methods have identified the earliest, most definitive cognitive and behavioral symptoms of illness, contributing to the identification, staging, and tracking of disease. With increasing public awareness of dementia, disease detection has moved to earlier stages of illness (e.g., Mild Cognitive Impairment), at a time when deficits are both behaviorally and pathologically selective. Neuropsychological studies show that cognitive deficits associated with Mild Cognitive Impairment and Alzheimer's disease (AD) are distinct from age-associated cognitive decline. Quantitative and qualitative differences are apparent across many cognitive domains, but are especially obvious in episodic memory (particularly delayed recall), semantic knowledge, and some aspects of executive functions. Recently, neuropsychological assessment was proven to be more responsive than MRI measures of brain atrophy for detecting disease progression in memory clinic patients with MCI or AD. Further, recently developed AD "biomarkers" are mainly utilized for research purposes. Clinical neuropsychologists are clinical psychologists who have completed doctoral and usually post doctoral training (fellowship) to obtain further training in neuroanatomy, neuropathology, and behavioral neurology following the completion of their clinical psychology specialization. A typical neuropsychological evaluation for a patient with dementia will last 2 or 3 hours, depending on the patient's tolerance, and will involve standardized testing of memory, attention, processing speed, language, visual spatial skills, executive functioning, and motor skills. By examining the patient's pattern of performance, neuropsychologists can help specify both the type of dementia experienced by the patient and the prognosis. In this paper we provide an overview of the pathognomonic neuropsychological features of AD dementia and how these differ from "normal," age-related cognitive decline. Further, we present guidelines for a screening evaluation and a comprehensive neuropsychological evaluation in MCI and AD dementia.

Introduction

There is no bright line distinguishing aging from dementia. Part of the challenge in defining this boundary has been the fact that neuropathologic features of degenerative diseases do not always predict neurocognitive or neurobehavioural expression. Many individuals experience profound dementia symptoms in life, but have modest neuropathological features of Alzheimer's disease (AD) on autopsy. In contrast there are individuals with relatively few dementia symptoms throughout life who on postmortem examination are found to have unequivocal neuropathological AD [1]. Nevertheless, clinicians are fully aware that dementia-associated diseases, such as AD, can begin decades before they are clinically obvious, and, once diagnosed, endure for many more years. Moreover, there is general consensus among clinicians and researchers that patients who are destined to develop AD will pass through an intermediate phase during which they experience symptoms which do not meet the criteria (functional or other) for a diagnosis of dementia [2]. In this respect, numerous terms and concepts have been used to describe this nether region. A concept that has gained wide acceptance based on the explosion of research on genetic, imaging and biomarker correlates of AD since the publication of the McKhann et al., [3] original AD criteria is Mild Cognitive Impairment (MCI). According to Petersen & Negash [4] "MCI refers to the transitional state between the cognitive changes of normal aging and very early dementia". In 2008, Petersen & Negash [4] proposed various clinical subtypes of MCI in order to broaden the concept and to include prodromal forms of a variety of dementia syndromes (Table 1). Prevalence rates of MCI vary widely, mainly due to methodologic differences. A recent large community-based study in individuals aged 70-89 years [5] noted a prevalence rate of 16%. Amnestic MCI patients were 2.3 times more common than nonamnestic, with the amnestic multidomain subtype appearing to be the most common and single-domain MCI least common. Moreover, individuals diagnosed with MCI have elevated rates of conversion to dementia, but considerable controversy exists regarding the percentage [6]. The conversion rates by subtype also remain controversial. A metanalyis [7], however, found rates of 11.7% for amnestic MCI (9 studies), 12.2% for amnestic multidomain (8 studies), and 4.1% for nonamnestic MCI. The probability of conversion also appears to be related to the number of cognitive deficits and studies have shown that individuals, who presented with multiple cognitive deficits earlier, including language, converted faster and were more likely to develop AD [7, 8]. Recently, a revision to the MCI criteria due to AD was provided [9], which relies on biomarkers for improving disease detection, diagnosis, and predicting clinical outcomes. Unfortunately, this

increased sophistication in the application of genetics and biomarkers has not been met with concomitant sophistication in profiling neurocognition. MCI diagnosis therefore, still relies largely on the use of self-or-informant related cognitive complaints, clinical judgement of cognitive and functional abilities, and objective evidence of minimal (mild) cognitive impairment on brief cognitive screening measures or neuropsychological assessment. Recently, Petersen, et al., 2014, [10], commented that, although the MCI concept has evolved over time, the "core criteria have remained unchanged"

Table 1. Subtypes of Mild Cognitive Impairment (MCI) [16

Amnestic MCI Single Domain	Subjective or proxy cognitive complaint; objective memory impairment; intact cognitive function; relatively intact functional ability; not demented
Amnestic MCI Multiple Domain	Subjective or proxy cognitive complaint; objective memory impairment and at least one other cognitive domain; intact cognitive function; relatively intact functional ability; not demented
Nonamnestic MCI Single Domain	Subjective or proxy cognitive complaint; objective impairment in one nonmemory domain; intact cognitive function; relatively intact functional ability; not demented
Nonamnestic MCI Multiple Domain	Subjective or proxy cognitive complaint; objective impairment in two or more nonmemory domains;intact cognitive function; relatively intact functional ability; not demented

As is the case with MCI a plethora of research has investigated methods for improving disease detection and diagnosis in AD. The impact of this research is evident in a recent revision to the criteria for AD proposed by McKhann et al., 2011 [11]. Although these criteria similarly to those proposed for MCI rely to a greater extent on biomarkers [12] (see Table 2) for improving disease detection and diagnostic utility, serial neuropsychological (neurocognitive) testing remains essential for profiling cognition. Moreover, the dermination of deficient functional capacity in usual daily activities requires clinical judgement by a skilled clinician.

Table 2. Biological and Neurosycholgical biomarkers potentially usefull in predicting conversion from MCI to AD: [12, 24]

Clinical	**Cognitive:** Amnestic MCI **Neuropsychiatric:** Depression, apathy, possibly nighttime behaviors and anxiety
Neuropsychological tests	Reduced performance in both **cognitive screening tests** (CDT, MMSE < 26, MoCA <22) and **specific neuropsychological tools** detecting multiple domain MCI (deficit of episodic memory combined with impairment of executive function for eg., RAVLT, SRT, TMT-B, SDMT, ADAS-Cog total score, New York University Paragraph Recall Test (Delay recall)
Neuroimaging	**MRI:** Selective atrophy in the medial temporal lobe (hippocampal atrophy, entorhinal cortex), posterior cingulate and orbitofrontal cortex **PET:** amyloid imaging, hypometabolism in Medial temporal region, hypometabolism in parietotemporal association cortex as marker of synaptic dysfunction, and posterior cingulate cortex
CSF markers	**Increase:** t-tau, p-tau **Decrease (Low):** Aβ 42 (marker of neuronal injury)
Genetic markers	ApoE e4 carriers

In 2013, the DSM – V [13] diagnostic criteria for neurocognitive disorders were released. These criteria provide a new context and incorporate many changes from the previous edition - including an increased reliance on cognitive assessment. Disorders that entail neurocognitive dysfunction are now termed " neurocognitive disorders" (NCDs). Broadly defined, major and mild NCDs serve as the primary disorders of cognition in the DSM-V and account for most aging-related neurocognitive syndromes. As mentioned previously diagnostic classification relies upon the use of neurocognitive test data across several well-delineated domains, with increased specificity afforded for the extent of neurocognive function and everyday dysfunction (see DSM-V, APA, 2013, for details regarding these diagnostic criteria and their etiological subtypes) [13].

In this paper we review the pathognomonic neuropsychological features of MCI due to AD neuropathology and AD dementia and how these differ from "normal," age-related cognitive decline. Further, we present guidelines for a screening evaluation and a comprehensive neuropsychological evaluation in detecting MCI and Alzheimers dementia

Neuropsychological features of MCI and AD

Neuropschological research on dementia has focused on AD because it is the most common cause of dementia and is primarily defined by its impact on cognition. AD is an age related degenerative brain disorder characterized by progressive cognitive decline and a broad spectrum of neuropathology, including neuronal atrophy, synapse loss and abnormal accumulation of amyloidogenic plaques (fibrillar amyloid-β protein in plaques and vessels) and neurofirillary tangles in the medial temporal lobe limbic structures (MTL) (e.g., entorhinal cortex, hippocampus) and the association cortices of the frontal, temporal, and parietal lobes [14]. Although there are variants of AD, a typical presentation involves an insidious onset, initial symptoms of episodic memory impairment – verbal and visual (i.e., deficient consolidation, rapid loss of new information, for eg., forgetting where the car is parked, getting lost, been repetitious) that is consistent with evidence of early changes in MTL structures. A wealth of evidence exists regarding the neuroanatomic basis of AD and MCI in relation to cognitive and biomarker changes (see Caraci et al., 2014 and Risacher & Saken, 2013, for a comprehensive review on the issue [12, 15].

As the neuropathology of AD spreads beyond MTL structures to the association cortices of the temporal, frontal and parietal lobes a gradually progressive course evolves to include other higher order cognitive domains/abilities [12 -14]. AD patients develop a semantic memory deficit that manifests as a loss of general knowledge and impairment of language abilities (i.e aphasia). These patients are also often impaired on tests of confrontation naming, verbal fluency, and semantic categorization, and show a reduced ability to recall overlearned facts (e.g., the number of days in a year) [12, 16].

Similarly, loss of knowledge is thought to contribute to the severe deficit experienced by AD patients in their ability to remember past events (i.e., retrograde amnesia) [12, 16]. Deficits in executive functions responsible for concurrent mental manipulation of information, concept formation, problem solving, and cue-direct behavior occur early in the course of AD. Patients with AD are impaired on difficult problem solving tests such as the mWCST, Tower of London, tests of relational integration (see Lezak et al., 2012) [17] and other executive function tests such as Part B of the Trail Making Test and Ravens Progressive Matrices [17]. Deficits in attention and visuospatial abilities develop during the course of AD, but are usually less salient than other cognitive deficits in the early disease stages. When they do occur, they are usually evident on dual processing tasks (shifting attention) and working memory tasks dependent upon the control of attentional resources [16,17]. Visuospatial deficits usually affect visuoconstructional abilities and are usually evident on tests such as the Clock Drawing Test, Block Design Test and complex figure copying (i.e apraxia), and visuoperceptual tasks tapped by tests such as the Judgement of Line Orientation [17]. In a small proportion of cases, AD may present in an atypical fashion with predominant deficits in language (i.e., logopenic progressive aphasia – LPA, executive function, motor function deficits (i.e., corticobasal syndrome) or vision (i.e., posterior cortical atrophy [11, 18].

As mentioned previously, MCI has been considered a precursor of AD, and it is now apparent that individuals with amnestic MCI are more likely to progress to dementia of AD etiology [11]. Results of a meta-analysis based on longitudinal studies, noted that 90% of those who converted had the amnestic MCI subtype [16]. However, whether a “pure amnestic subtype” exists remains a controversy and requires further investigation. Several studies have also noted that amnestic MCI patients who converted to dementia had lower executive function scores at baseline [16, 17]. Moreover, various language deficits been reported in naming and word retrieval, verbal fluency, language comprehension, discourse processing, and the ability to define words [16,17]. In 2009 Oulahaj et al., [19] noted significant sensitivity of language test scores in detecting early markers of later conversion to AD. They noted that although episodic memory impairment is the core deficit of amnestic MCI, their findings on the expression subtest of the Cambridge Cognitive Examination (CAMCOG), which includes verbal fluency, spoken language descriptions, definitions and comprehension was a stronger predictor of duration to conversion than either learning or memory subtests.

Differentiation of age-related cognitive decline and early / mild dementia

Although the pattern of progression of AD pathology is not fully known, as noted previously evidence suggests that the earliest changes occur in medial temporal lobe structures, critical for episodic memory [6, 8, 14]. Clinical utility studies of episodic memory measures for the early detection of AD have identified a number of characteristics noted to be effective in discriminating mildly demented patients and healthy older adults. Firstly, very early AD patients are impaired on measures of delayed recall (i.e., show abnormally rapid forgetting). More specifically, there are reports that absolute delayed recall scores (i.e., amount recalled after the delay divided by the amount recalled on the immediate learning trial) differentiated mild AD patients from healthy elderly with 85 - 90% accuracy [20]. Secondly, to be-remembered information is not accessible after a delay even if retrieval demands are reduced by the use of recognition cues/testing. Thirdly, AD patients exhibit an abnormal serial postion effect characterized by an aatenuation of the primacy effect (i.e., recall of words from the beginning of a learning list), suggesting ineffective transfer of information from primary to secondary memory. Fourthly, AD patients show an enhanced tendency to produce intrusion errors (i.e., producing previously learned information during their attempt to recall new material on both verbal and non verbal tests, presumably due to increased sensitivity to interference and /or decreased inhibitory processes [14, 17, 20].

From a neuroimaging perspective structural MRI and especially hippocampal volumes of AD patients are 10-12% smaller than those of age-matched controls in the early AD stages (MMSE score approximately 27), whereas they are 15-30% smaller in mild AD (MMSE approximately 20) and 30-40% smaller in moderate stages

(MMSE approximately 15) [23]. Furthermore, MTL atrophy distinguished AD from age-matched controls with sensitivity and specificity over 85% and predicted conversion of MCI patients to AD with 75-80% accuracy [23]. The authors make a note however, that MTL atrophy is not a marker specific to AD, since decreased hippocampal volumes may be seen in other neurodegenerative diseases, depression and even normal aging. They suggest that the rate of hippocampal atrophy is possibly a better indicator of AD pathology, as hippocampal loss is two to four times faster in AD patients compared to demographically matched controls [23].

Although significant progress has been made in identifying the typical pattern of cognitive deficits associated with early AD, the boundaries between normal aged – related cognitive decline/change and early signs of AD remain especially difficult to delineate in the very elderly (i.e., over age of 80). This is due to similar and overlapping early structural and functional changes in normal aging and early AD. Normal aging is associated with mild brain atrophy and increased white matter abnormality seen on MRI neuroimaging. Moreover, f-MRI shows decreased hemodynamic response and reduced synaptic density is evident on histopathological examination [20, 21]. These neuroanatomic and neurofunctional changes are thought to mediate age-related decline in information processing speed, executive function, learning efficiency and effortfull retrieval [21]. In this respect, it becomes obvious that normal aging may detrimentally affect many of the same cognitive domains affected by AD, and the prominence of specific deficits related to AD may be much less evident in the older old (over 80) than in the younger old (below 70). This implies that the older old will show a less distinct and somewhat atypical cognitive deficit profile associated with AD, rendering differentiation with early AD a challenge for the clinician. Moreover, in this older age group there is significant risk of false negative diagnostic errors if the clinician expects to see the typical deficit pattern seen in younger AD patients. Therefore, accurate detection of AD in the older old requires a multifaceted approach to diagnosis with the integration of biomarker (neuroimaging, CSF, genetic) (see Table 2) clinical neuropsychiatric assessment, clinical neurological and geriatric evaluation and neuropsychological testing by an experienced clinical neuropsychologist [20 -22].

What is neuropsychological assessment?

As clinical neuropsychologists face the challenges of the future, their role in applying the understanding of brain-behaviour relationships to individuals with cognitive and behavioural problems in order to improve the diagnosis and treatment of these conditions has not changed. Although advances in structural and functional neuroimaging have greatly reduced the role of neuropsychology in localizing lesions (though not eliminated it), a new revelation that has come with more sensitive imaging technology is the vast difference noted in presentation of patients, even when their brain lesions show similar distribution/localization on neuroimaging. “Treat the patient, not the picture” is a common teaching point for neurologists, psychiatrists, and clinical neuropsychologists, and it is precisely that role that has defined the importance of comprehensive neuropsychological assessment of the patient [17, 21]. Clinical neuropsychologists are probably the “most ideal” clinicians in establishing whether cognitive deficits correspond to findings on neuroimaging and to determine whether neuropathology of the brain, neurodegenerative or other, is associated to neurocognitive and neurobehavioural disorders [15,17,21].

Neuropsychological assessment or assessment of cognition and behavior is critical to the diagnosis of MCI and dementia. A neuropsychological assessment entails a series of different tasks designed to probe specific aspects of cognition. For eg., in the recently published DSM-V, six independent, but cognitively overlapping domains are outlined for determining minor and major neurocognitive disorders. These incude complex attention, learning and memory (verbal and visual), perceptual/visuospatial/visuoconstructive, language, executive function and social cognition [13]. Neuropsychological tests are intrinsically performance-based. Self – reports of functioning, as well as observations of behavior while performing testing, are also critically important pieces of information. Differential diagnosis, however, is much more challenging for most conditions. Although neurologists and psychiatrists may suspect cognitive dysfunction following a careful clinical examination, only objective cognitive testing may quantify the extent, severity and pattern of deficits and assist in establishing functional capacity. Moreover, as the severity and pattern of cognitive decline may evolve over time, especially in neurodegenerative disorders, revision of the diagnosis may be required, for eg., conversion of MCI to dementia.

The pattern of cognitive deficits determined through neuropsychological assessment provides insight into normal brain functions and the pathological processes involved. However, results obtained from neuropsychological testing have to be interpreted within the broader context of patient – family history, medical, psychiatric, neurological examination, neuroimaging and laboratory (eg., blood, genetic) tests [17]. Moreover, various medical and non-medical variables may influence neurocognitive performance (e.g., reduced effort – motivation during testing, comorbid medical or psychiatric – neurological conditions (e.g., depression, anxiety, respiratory, hepatic, drug intoxication, sleep deprevation). Non appropriate communication between the clinician and patients, cultural bias and illiteracy or very low levels of education may also negatively affect cognitive performance. Language deficits which are common especially in dementia syndromes may also interfere with the evaluation of non-language cognitive domains. Importantly, all scores obtained in cognitive testing need to be compared with appropriate culturally and demographically adjusted (age, education, gender and sometimes intelligence) normative data derived from large samples of healthy individuals. Alternativelly, performance can be roughly compared to the estimated cognitive ability of the individual patient, based either on a reading task or educational/vocational attainment. A disproportiniate impairment in one or more cognitive domains, while not pathognomic in itself, may signal a disorder of cognition and require careful determination of the pattern of deficits which is diagnostically more informative.

In the following sections we will provide background on common neuropsychological tests used in evaluating patients with MCI and AD dementia, and brief tips on how to interpret such results when assessing these patients. We also provide guidelines for a screening evaluation and a comprehensive neuropsychological evaluation in MCI and AD dementia.

Assessment of cognitive disorders in MCI due to AD and Alzheimers Disease: a neuropsychological perspective

Cognitive screening

Assessment of cognition is critical to the diagnosis of MCI and AD dementia as noted previously by the recently developed criteria for these two conditions [9,11,13]. However, diagnosis of MCI and AD dementia is based on clinical neurological / psychiatric evaluation, personal and medical history, performance on neuropsychological tests, laboratory and neuroimaging findings, perceptions of families and patients and functional capacity. Although a vast array of neuropsychological tools for assessing cognition in MCI and dementia are available, not all potential MCI or AD patients will undergo a comprehensive neuropsychological assessmemt. This is because it is not always possible due to time restrictions or inability of the individual to complete such an evaluation, or not always necessary. More specifically, busy clinicians or physicians without neuropsychological experience may find time and learn how to administer a brief cognitive screening test, which may provide an estimate of overall cognitive ability/function and assist in identifying patients who require comprehensive neuropsychological assessment. In the case of assessing potential MCI due to AD several screening measures are available with potentially satisfactory psychometric properties (see http: //pad 2020.org) for details regarding the Snyder et al., 2011 [25] survey that provided a comprehensive review and compared the psychometric properties of these measures. In Table 3, listed below, we provide brief information on the most common screening measures utilized internationally in the assessment/detection of potential MCI due to AD and AD. Where a Greek adaptation of the measure is available, this has been noted. For a comprehensive review of these measues refer to [12] or the relative publications of the measures noted in the references/bibliograpgy.

Table 3. Common screening measures used in detecting MCI due to AD and AD [26 -32

Screening Measure	*Description*	*Reference*
Mini Mental State Examination (MMSE)	The most recognized and widely used cognitive screening test. MMSE [26] was designed to differentiate cognitive impairment due to dementia from cognitive impairment in psychiatric illness. Adminastration time is less than 10 minutes. However the test was not designed to distinguish different forms of dementia and it is heavily weighted towards the orientation/attention and memory domains (70% of the score). Asessments of language and visuospatial function are very brief, and there is no assessment of executive function. In this sense it is insensitive to some types of dementia (for eg., frontotemporal). Recent meta-analytic report noted that the MMSE " has very limited value in making a diagnosis of MCI against healthy controls... [16, p 159]. The MMSE has a maximum score of 30 points, with a score of below 25 considered impaired. For the *Greek validated version* [27] at the suggested cut off score level of 23/24, sensitivity is 90.80, specificity 90.62.	** [26,27]
Montral Cognitive Assessment (MoCA)	The MoCA is a more recent screening tool published in 2005 [28]. Compared to the MMSE, attention and memory make up only half of the maximum 30 points, whereas language, executive function and visuospatial abilities are also tested. Recent studies [29,30] indicate that the MoCA is superior to the MMSE in detecting Mild cognitive impairment. Its administration time is comparable to that of the MMSE.	** [28, 29,30]
Addenbrooke's cognitive examination-III (ACE-III) *Addenbrooke's cognitive examination-revised (ACE-R) Greek validated version*	The ACE, now in its third revision, is the most detailed cognitive screening test and is widely used [31]. Similar to the MoCa, it covers a relatively wide range of cognitive domains, including attention/concentration, memory, verbal fluency (executive function), language and visuospatial ability. It is scored with maximum 100 points and a suggested cut -off score of < 88/100 detects dementia with high sensitivity and specificity. Moreover, it has the advantage of being able to distinguish dementia subtypes by considering the pattern of cognitive deficits and not just severity of impairment. It has been reported to differentiate FTD and AD [31], primarily due to detailed language and executive function assessment. A Greek validated version of the ACE-R is available and has been reported to have very good psychometric properties with excellent diagnostic / discriminatory accuracy for AD and FTD patients [32]. The ACE was recently made available in an electronic (tablet version) (see http://www.acemobile.org).	[31,32]

**Greek edition available Source

Although the previously mentioned screening measures do have good psychometric properties and even sufficient utility in some cases, it is important to remember that they may not be sensitive to subtle cognitive decline, especially in individuals with high intelligence or education levels and those with high cognitive reserve [17]. In this respect, caution should be taken by physicians to refer potential patients requiring more detailed assessment to a clinical neuropsychologist for a comprehensive evaluation.

Comprehensive Neuropsychological assessment

A comprehensive neuropsychological evaluation may take between 2- 5 hours depending on the abilities of the individual to be tested, the presenting symptoms and severity of deficits. Although separate measures (tests) may be used to probe each cognitive domain independently, in practice, most cognitive tasks are not "pure "measures of a single cognitive domain. Therefore, reliable performance should be based on interpreting the combined battery of tests, whether these are chosen via a "flexible" battery approach or fixed battery. It should be noted that very few clinicians today still use a fixed battery (for e.g., Halstead Reitan Battery), maybe 10% of practicing neuropsychologists. The majority use flexible battery, meaning a battery put together to best address the condition at question (TBI, Dementia) or population (older adults, younger adults) or setting (input, output) [17].

The neuropsychological assessment should be initiated with an assessment of attention and concentration, as cognition may be considered hierarchial, implying that satisfactory attention and concentration are necessary prerequisites for evualating other cognitive abilities. Orientation should also always be tested in dementia assessment before moving on to other cognitive tasks. Individuals that are disorientated and unable to concentrate on the cognitive tasks at hand will most probably not complete the assessment or their results will be uninterpretable. As such, concentration is investigated first, either by assessing ability to respond to simple questions or commands (provided language capacity is intact), or by observing distractibility, lethargy and drowsiness during interaction [17, 33. Table 4 provides examples of common measures used in the neuropsychological assessment of MCI due to AD and AD.

Estimation of premorbid cognitive function

Premorbid general cognitive function provides an internal benchmark against which performance on neuropsychological testing can be interpreted. Highly intelligent individuals usually perform better on cognitive tasks, even during early dementia stages. Premorbid cognitive capacity may be estimated through vocational and educational attainment or by assessing word reading ability, which reflects lifelong learning/knowledge capacity and is relatively resistant to the effects of aging and cognitive decline. For English speaking individuals, the National Adult Reading Test (NART), composed of 50 irregular words of decreasing frequency may be used. This task is based on the fact that pronunciation and knowledge of irregular words, which cannot be read correctly with the application of common phonetic rules, can be acquired only through exposure and correlate highly with general intelligence levels [17,33].

Attention and Concentration

Simple attention is usually preserved, at the least in the initial stages of AD. AD patients with mild dementia do not show impaired performance in span tasks despite the fact that they obtain poorer results than patients without dementia. Digit forward span, examines the ability to sustain attention, with the longest sequence of digits that a subject can repeat at a time. For healthy individuals this stands between five and seven digits. The Backward digit span task is the longest sequence of digits that a subject can repeat in reverse order, and involves other components such as working memory. Backward span length is usually one digit less than forward span. An analogous visual modality task is the Corsi block tapping task, in which the subject must repeat a sequence that is visually presented by the examiner in a board with blocks. The largest consistent difference between AD patients and controls has been noted in the backward visual span task, Another more complex timed attention task is the Trail making test. This task composed of two parts requires mental flexibility and increased working memory. Both parts are found impaired in AD subjects, however, Part A, is influenced by decrements in motor speed and visual tracking and part B by executive function difficulties. Similar results have been found in the Symbol Digit Modalities Test, another timed task that requires attention, executive function and motor execution abilities to be completed.

Memory

Memory is conceptualized in different ways such as declarative or explicit or implicit (memory for skills or procedures). Declarative memory is further subdivided into *episodic* (where you bought your electronic tablet from last summer) or *semantic* (knowledge of the Greek Mountains). Generally, only declarative, particularly episodic memory (verbal and visuospatial/non verbal) is routinely tested in clinical settings that evaluate potential MCI and AD patients. Most memory tests assess various components summarized as follows: *encoding* (i.e., capacity to take in novel information), *retention* (i.e., capacity to hold this information over time), and *retrieval* (i.e., capacity to bring back this information after a delay period). Retrieval can also be examined using free recall (no external assistance), cued recall (in response to a cue) or recognition. Generally, free recall is more difficult than cued recall, which in turn is more difficult than recognition [33, 34].

Table 4. Common measures used in the neuropsychological assessment of MCI due to AD and AD [38-46]

Measure	*Description*	*Reference*
Episodic Memory	Free and Cued Selective Reminding Test Rey Auditory Verbal Learning Test California Verbal Learning Test Logical Memory I and II of the Weschler Memory Scale Visual Reproduction Subtests of the Weschler Memory Scale	** [38 -40]
Executive Functions	Trail Making Test Set-shifting tasks Reasoning tasks Problem solving tasks Planning tasks	** [41-44]
Language	Boston Naming Test Letter and Category fluency tasks Expressive Speech and Comprehension tasks	**[45-46]
Visuospatial Skills	Figure copying tasks	
Attentional Control	Digit Span Forward Simple and divided attention tasks	

**Greek edition available Source

In accordance with the initial involvement of the medial temporal lobe, cognitive changes in AD start with specific difficulties in encoding and retention / storage of new information. In clinical practice, verbal memory is tested by utilizing prose passages (e.g., Weschler Memory Scale - Logical Memory), pairs, arrays or lists of words with variable semantic relations (e.g., Paired- Associate Learning, Rey Auditory Verbal Learning Test (RAVLT), Free and Cued Selective Reminding Test (FCSRT). Most of these tests include immediate and delayed (i.e., after 25 -30 min), recall (free and/or cued) and recognition components. These particular memory deficits can be optimally detected with memory tests that enhance mnemonic retrieval by means of encoding specificity techniques such as the one utilized by the Free and Cued Selective Reminding Test (FCSRT). This test appears to be particularly sensitive in differentiating episodic memory deficits due to mild cognitive impairment from those due to early AD, and in differentiating AD from FTD [35, 36]. Low scores can be the expression of genuine memory deficits but can be also affected by other conditions such as attentional problems observed, for example, in depressed patients or the difficulties in retrieval that are usually found in other entities such as frontotemporal dementia. The FCSRT as mentioned previously overcomes this limitation by applying the concept of encoding specificity, during learning and recall, which ensures that subjects pay attention to the material and, at the same time, facilities posterior retrieval. Encoding specificity implies that information is processed in a precise manner (i.e., semantically) during the process of learning. Interestingly, AD subjects do not seem to benefit from the facilitation produced by this technique due to the genuine deficit in encoding and storage processes that they have. Thus, the use of encoding specificity technique maximizes the sensitivity of the memory task to detect AD [34 -36]. Visuospoatial memory is assessed by recognition of visual stimuli or by recollection/reproduction of line drawings from memory. Semantic memory is generally examined with tests of word knowledge, knowledge of famous faces or less commonly world events [see 17 for further details].

Language

Language skills in AD can be examined using different tasks such as spontaneous speech assessment, repetition, comprehension and reading. The presence of anomic aphasia, with fluent but abnormal language output along with preserved repetition, is common as are word finding deficits. The nature of deficit is still not clear, although either the loss of semantic representations in memory and/or executive difficulties to access this information are proposed as the probable problem underlying word-finding deficits. Comprehension deficits in AD include difficulties at the semantic, syntactic and metaphorical verb. For a review on language assessments in AD see this issue (Kambanaros et al., 2015, this issue) and [17, 33].

Executive function

Executive function comprises different cognitive skills including the ability to abstract, shift set, plan, organize and adapt behavior to current circumstances and is tested utilizing a combination of approaches. For example, abstraction can be tested by concept formation or similarities tasks (For example, abstraction can be tested by concept formation or similarities tasks (e.g., ‘’what do ‘bicycle’ and ‘train have in common?’’). The type of responses will inform the examiner as to the capacity of the patient to reason in abstract terms (e.g., ‘They are both modes of transport’) or in concrete terms (e.g., ‘They both have wheels’). Set shifting can be tested using the Trail Making Test. Part A of the Trail Making Test requires the participants to draw lines between circles labeled with consecutive numbers (i.e. ‘1’, ‘2’, ‘3’, etc). In Part B, the task is made more difficult by alternating consecutive numbers with consecutive letters (i.e. ‘1’, A, ‘2’ ‘B’, ‘3’, ‘C’, etc). Individuals with executive impairment may take longer to complete these tasks, or make errors or both. Fluency tasks, such as letter (e.g. F, A and S), or category (e.g. animals, vegetables) fluency, also assess capacity to follow specific rules and to modify behavior flexiblly (i.e. set shifting). Fluency tasks require the generation of as many words as possible in 1 min according to the rule set. Patients with

executive dysfunction produce fewer correct responses on verbal fluency tasks than normal controls, although language proficiency and/or deficits need to considered. Other, non-verbal equivalents (e.g. desing fluency) also exist, but are not common used. Planning and organisation deficits might become apparent by observing the approach taken to complete a task. For example, a slow and disorganized approach to a copy task might suggest executive impairment. Disinhibition, and behavior modulation more generally, is infrequently tested in clinical practice. One option is the Hayling Sentence Completion test, which requires suppression of a prepotent response by completion of sentences with non-sensical endings. A number of different aspects of executive functioning including temporal judgement, set-shifting, planning and strategy can be tested formally using measures such as the Behavioural Assessment of the Dysexecutive syndrome (BADS). More complex tasks such as the Iowa Gambling Test, or the Wisconsin Card Sorting test, are used infrequently, either in a research setting or sometimes clinically, to detect subtle executive dysfunction [17,33].

Visuospatial and constructional tasks

Visuospatial function is assessed by measuring ability to interpret various types of visual information. Simple copy or drawing tasks, such as interlocking pentagons, wire cube, interlocking figure of eights or the reproduction of a clock face, are widely used to assess constructional ability. Another common and more difficult task of visuoconstructive ability is the Rey – Osterrirth Complex Figure Task, where the person is asked to copy complex line drawings. Basic visual processing can be assessed using line bisection or object cancellation tasks. Another common test, the Visual Object and Space Perception Battery (VOSP), involves the interpretation of information that varies in visual complexity (eg., dot counting, position discrimination and cube analysis). Cognitively, intact individuals are expected to obtain perfect, or near-perfect, scores on VOSP subtests (>90% correct). As such, even a small decline in performance is suggestive of cognitive impairment [17,33].

Conclusions

The cognitive expression of MCI due to AD and AD is closely related to the topography and progression of brain neuropathology. Cognitive changes in AD are usually initiated with memory difficulties, although atypical forms have been characterized. Memory impairment in AD is specific, focusing on encoding and storage of new information. This type of memory impairment can be optimally detected with memory tests that enhance mnemonic retrieval by means of encoding specificity techniques. Despite the prominence of memory impairment, other cognitive domains, in particular executive function, attention and praxis, should be assessed as they appear to be impaired parallel to the progressive course of AD. Like many other clinical tools, a comprehensive neuropsychological assessment can play a central role in the diagnosis and grading of cognitive deficits in AD dementia and its intermediate stage MCI. Moreover, an understanding of cognitive (e.g., orientation, attention, memory, language, visuospatial function and executive function) and behavioral domains is central to the interpretation of neuropsychological reports. It is important, however, to keep in mind that, the selected tests used in all cases should be adapted and standardized to the studied population. Furthermore, the pattern of deficits can be helpful in defining clinical phenotypes, which can assist in predicting the underlying molecular pathology. Given the consistent findings that cortical degenerative changes are often found at postmortem in individuals who had no observational evidence of deteriorated cognitive functioining during life, there is considerable need to perform comprehensive neuropsychological assessments. Although recently developed AD “biomarkers” are now available to assist in diagnosis and differential diagnosis of AD dementia, these are still unavailable in many clinical settings and are utilized mainly for research purposes. Moreover, neuropsychological assessment was proven to be more responsive than MRI measures of brain atrophy for detecting disease progression in memory clinic patients with MCI or AD. At this time neuropsychological assessment has many uses and adds critical information to the neurological, psychiatric and neuroimaging assessments of MCI and AD patients.

The authors declare that they have no conflicts of interest.

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Arizona battery of communication disorders of dementia for evaluation of cognitive impairment in PD and early diagnosis of PDD

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Abstract

The present study investigated the utility of the Arizona Battery of Communication Disorders of Dementia (ABCD) in detecting cognitive - communication decline in PD patients and its ability to differentiate PD patient's performance from patients with Parkinson's disease dementia (PDD) and Alzheimer's disease (AD). The ABCD was administered to 122 age and education matched participants [60 cognitively healthy controls, 20 Alzheimer's disease (AD), 18 PD and 24 PDD patients]. Additionally they were administered the Greek versions of the Mini Mental Status Examination (MMSE), Abbreviated Mental Test Score (AMTS), 15 item Geriatric Depression Scale (GDS -15), Hellenic Neuropsychiatric Inventory (H-NPI), and Clock Drawing Test (CDT). ANOVA and Receiver Operating Characteristic (ROC) analyses were then performed. These analyses revealed significant differences in various ABCD subtests between PD and PDD patients, favoring the PD group. Non demented PD patients performed significantly worse than cognitively healthy controls in 5 of the ABCD subtests, while the PDD group performed significantly worse than cognitively healthy controls in most of the ABCD subtests. Not surprisingly, the PDD group differed significantly from the AD group in the majority of the ABCD subtests, providing further evidence regarding the different clinical profile of these dementia subtypes (cortical vs. subcortical pattern). Moreover, the ABCD showed better discriminatory utility compared to the MMSE in detecting cognitive decline in PD patients.

Introduction

Parkinson's disease (PD) has been largely considered a neurodegenerative motor disorder [1-3]. Although in the past patients with Parkinson's disease were considered to remain cognitively intact, it is now well established that they show cognitive decline [4-6].The occurrence of dementia in Parkinson's disease (PDD) has an average prevalence rate of 40% [7]. Dementia occurs in the majority of PD patients [8,9], and many factors contribute to this, mainly the age at onset of disease and its duration [10-12]. Cognitive decline as a manifestation of idiopathic PD [6] is faced in clinical practice and elderly individuals with PD are at a 6-fold risk of developing dementia compared with age-matched (non-demented) healthy subjects [10]. PD dementia and dementia with Lewy bodies (DLB) have many similarities, but differ in contrast to AD patients [4, 13]. Further, PDD is not well characterized in the literature, and the relationship of PDD to Alzheimer disease remains unclear [3]. PD patients may also show decline in various cognitive domains, and some researchers believe that the cognitive deficits seen in PD and PDD have only quantitative and not qualitative differences. Furthermore, neuropsychological studies such as Janvin et al., reported that 26% of PDD patients exhibit similar patterns of cognitive impairment to those observed for patients with AD [14]. The occurrence of dementia influences not only the quality of patients' [15,16] and their families life (institutionalization and healthcare costs) [17], but also the prognosis, especially once they have progressed to the final stage of the disease (mean survival after PDD diagnosis is 3-5 years) [18].

Another reason that makes early diagnosis beneficial is that rivastigmine and donepezil, the cholinesterase inhibitors which are the mainstream of medical treatment in AD, have been shown to benefit PDD patients as well [19]. Many studies have used different types of assessments and battery of tests in order to evaluate cognitive and language abilities [20-23] or assessment protocols [24] that report prediction of cognitive decline or association with mild dementia in early Parkinson's disease. Kandiah, et al. (2014) [25] reported that the use of a single test, specifically the Montreal Cognitive Assessment (MoCA) can reliably predict cognitive decline in early PD. Also a recent report revealed that an early diagnosis of PDD may be established with Single Photon Emission Computerized Tomography by detecting dopamine transporters (DaT-scan SPECT) and neurological examination [26]. Pfeiffer et al (2014) [27] noted, with the use of neuropsychological tests, that 34% of early-stage PD patients exhibit cognitive impairment.

In the present study we compared the cognitive and communication performance of demented and non-demented PD patients, AD patients and cognitively healthy controls by utilizing the Arizona Battery of Communication Disorders of Dementia [28]. Furthermore, we investigated whether performance on this battery of tests can discriminate between PD and AD dementia.

Material and Methods

Participants

We recruited 20 patients diagnosed with Alzheimer's disease (AD), 18 patients with Parkinson's disease (PD) and 24 patients with Parkinson's disease dementia (PDD). We further recruited 60 cognitively healthy participants matched for age and education to the clinical samples. Patients were recruited from the University Hospital of Ioannina Neurology Department's outpatient clinic. All patients were diagnosed after consensus by a multidisciplinary group of clinicians specializing in movement disorders. PD and PDD patients were diagnosed according to criteria stipulated by the Movement Disorder Society (MDS) [12, 29]. PD progression was defined according to Hoehn and Yahr staging (1967) [30]. AD was diagnosed according to National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease [31].

To ensure that we compared only the mild forms of PDD and AD, only patients with Geriatric Depression Scale (GDS-15) score of ≤7, and Mini Mental Status Examination (MMSE) score 20 - 24 were judged eligible for the study. Participants with a history of neurological impairments including head trauma, epilepsy, and stroke or brain surgery and non-native Greek speakers were excluded. Participants signed informed consent forms, and the ethics committee of the institution approved the protocol. All scales were administrated in one session lasting approximately 1 hour.

Assessment of Cognitive Function

In order to evaluate the cognitive level and to categorize participants, the Greek adapted edition of the Mini Mental Status Examination (MMSE) [32-33] was administrated. MMSE is a widely used scale, which assesses orientation, verbal memory, language, attention/calculation, and visuoconstructive abilities. The MMSE is recommended by the Movement Disorder Society Task Force for level I testing, to assess PD associated cognitive decline [12, 29]. It has also been used to characterize levels of cognitive declination of PDD in clinical trials [19, 34]. Moreover, in order to assess cognitive function and visuospatial abilities, the Greek version of the Abbreviated Mental Test Score (AMTS) [35-36] and the Clock Drawing Test (CDT) [37-38] were administrated.

Assessment of Cognitive – Communication abilities

To assess the probable occurrence of cognitive - communication deficits, the Greek adapted version of the Arizona Battery for Communication Disorders of Dementia (ABCD) (Copyright © 1993 PRO – ED, Inc. *Arizona Battery for Communication Disorders of Dementia*, translated with permission of the publisher. All rights reserved), was administrated to all participants. The battery was translated and back translated in Greek and English, by three different individuals who were native speakers in both languages. The translated versions were then reviewed by a linguist and two speech language pathologists in order ensure proper cultural adaptation [39]. Generally ABCD is a standardized test battery for the comprehensive assessment and screening of dementia patients. It includes subtests that evaluate linguistic expression (object description, generative naming, confrontation naming, and concept definition), linguistic comprehension (following commands, comparative questions, repetition, reading comprehension – words and reading comprehension – sentences), verbal episodic memory (story retelling-immediate, word learning – free recall, word learning – total recall, word learning – recognition, and story retelling - delayed), visuo -spatial construction (generative drawing and figure coping), and mental status. Subtests can be given individually or collectively. The results obtained are useful for differential diagnoses, developing treatment goals and patient care planning, monitoring patient change over time, and discharge planning. The original ABCD was validated and standardized on Alzheimer's and Parkinson's disease patients.

Assessment of Neuropsychiatric Status

In order to exclude patients with major psychiatric disorders (e.g., with major depression or hallucinations) which may result in pseudo dementia, they were assessed psychiatrically and were also assessed with the Geriatric Depression Scale (GDS -15) [41], and the Hellenic Neuropsychiatric Inventory (H-NPI) [42-43].

Data Analyses

All statistical analyses were performed with the SPSS software version 20.0 package (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). The Kolmogorov – Smirnov method was applied in order to determine the distribution of the data. We found that our data was normally distributed and therefore proceeded with parametric tests. Analyses of variance with post hoc tests and independent sample t-tests were utilized for comparison of continuous variables. Statistical significance was assumed at a false detection rate of $p < .05$. Two tailed statistics were used throughout and $p < .05$ was considered significant. Receiver Operating Characteristic (ROC) analysis was used to evaluate the ability of the ABCD outcome measures (subtests) to discriminate participants with PD, PDD and cognitively healthy elderly and PDD from AD patients.

Results

Our initial analyses found that cognitively healthy participants and the clinical groups were not significantly different regarding demographic characteristics. Specifically, we found a non-significant group effect for age F (3, 118) =1.777, p = .285, education F (3, 118) =1.408, p = .666 and gender F (3,118) =1.214, p= .172 Moreover, PD and PDD patients did not differ significantly as regards Hoehn-Yahr staging, t (40) = 1.333, p = .483 (Table 1). On the other hand we found a significant group effect on the MMSE F (3, 118) = 75.096, p< .01, AMTS F (3, 118) = 33.073, p < .01, GDS F (3, 118) = 24.494, p< .01, and CDT F (3, 118) = 15.233, p< .01 (Table 2).

In order to determine the validity of the ABCD in discriminating between patient groups performance and from cognitively healthy participants, we conducted comparisons on the ABCD outcome parameters (subtests) between the groups (PD, PDD, AD patients and cognitive healthy participants). A one way ANOVA was performed for all ABCD's subtests which revealed a significant main group effect for mental status [F (3, 118) = 20.073, p < .01], story retelling (immediate) [F (3, 118) = 9.121, p< .01], following commands [F (3, 118) = 6.851, p< .01], comparative questions [F (3, 118) = 15.993, p< .01], word learning (controlled encoding) [F (3, 118) = 20.161, p< .01], word learning – free recall [F (3, 118) = 7.494, p< .01], word learning cued recall [F (3, 118) = 3.598, p< .05], ABCD's total recall [F (3, 118) = 6.654, p< .05], word learning – recognition [F (3, 118) = 13.646, p< .01], repetition [F (3, 118) = 58.276, p< .01], object description [F (3, 118) = 2.746, p< .05], reading comprehension (words) [F (3, 118) = 8.009, p < .01], reading comprehension (phrases) [F (3, 118) = 10.528, p < .01], generative naming (semantic category) [F (3, 118) = 3.357, p< .05], conformation naming [F (3, 118) = 9.154, p < .01], concept definition [F (3, 118) = 12.219, p< .01], generative drawing test [F (3, 118) = 3.6073, p< .05], figure copying [F (3, 118) = 9.983, p< .01], and story retelling (delayed response) [F (3, 118) = 10.203, p< .01].Descriptive statistics for outcome parameters in each trial of the RAVLT are presented in Table 3, including pairwise comparisons between the groups.

Table 1. Demographic data of participants: mean and standard deviation.

	Healthy Controls	PD	PDD	AD
Participants	60	18	24	20
Gender (M/F)	30/30	12/6	15/9	13/7
Age (years)	65.78 ± 6.76	67.34 ± 4.45	67.54 ± 3.54	68.08 ± 5.73
Education (years)	11.83 ± 4.56	11.35 ± 3.98	10.95 ± 3.68	10.12 ± 3.52
Hoehn-Yahr staging	----	1.67 ± .053	1.59 ± .038	----

Table 2. Clinical data of participants: mean and standard deviation.

	Healthy Controls	PD	PDD	AD
Participants	60	18	24	20
MMSE	28.93 ± 1.68	28.36 ± 1.90	21.58 ± 4.44	19.05 ± 6.26
AMTS	9.17 ± .834	5.88 ± 1.86	3.04 ± 2.81	6.69 ± 2.63
CDT	9.00 ± .612	9.00 ± .713	7.75 ± 1.22	5.92 ± 2.36
GDS	1.67 ± 2.56	3.82 ± 2.24	4.62 ± 3.53	4.66 ± 3.59

Furthermore, in order to determine whether the ABCD can discriminate between healthy cognitive participants and PD patients, we conducted an ROC analysis. Area Under Curve (AUC) an index of effect size was the primary outcome of this analysis. Results of this analysis are presented in tables 4 between controls and PD patients for the ABCD subtests and in table 5, for the ABCD constructs and total score. The ROC analysis revealed statistically significant positive effects in five of the nineteen ABCD subtests between non- demented subjects and PD patients. A high effect size was noted for the subtest "Following commands" (AUC .956, p< .01), while a medium effect was noted for the "Comparative questions" subtest (AUC .617, p< .05), "Word learning – free recall" subtest (AUC .736, p< .05), "Word learning – recognition" subtest (AUC .731, p< .05) and "Reading comprehension (words)" subtest (AUC .722, p< .05)(Table 4).

Regarding ABCD constructs we found a significant effect on the construct linguistic expression (AUC .762, p< .05) and ABCD total score (AUC .675, p< .05). The remaining three constructs were noted to have lower non-significant effects: mental status (AUC .589, NS), episodic memory (AUC .567, NS), linguistic comprehension (AUC .485, NS), visuospatial construction (AUC .675, NS) (Table 5).

Table 3. Pairwise comparison of ABCD subtests for all clinical groups and healthy controls.

	Controls & PD	Controls & PDD	Controls &AD	PD & PDD	PD &AD	PDD & AD
Mental status	.11 (NS)	4.34 (p < .01)	7.96 (p< .01)	3.87 (p< .01)	8.35(p< .01)	5.46(p< .01)
Story retelling (immediate)	.03 (NS)	3.76 (p< .01)	7.46 (p< .01)	3.73 (p< .01)	7.23(p< .01)	5.11(p< .01)
Following commands	1.26 (p< .05)	1.11 (p< .05)	2.57 (p< .01)	.24 (NS)	2.91.(p< .05)	2.36(p< .05)
Comparative questions	1.09 (p< .01)	1.23 (p< .01)	2.68 (p< .01)	.79 (NS)	1.71 (p< .05)	1.32 (p< .05)
Word learning (controlled encoding)	.11 (NS)	1.88 (NS)	4.14. (p< .01)	1.98 (NS)	4.64. (p< .01))	3.67. (p< .01)
Word learning – free recall	2.63 (p< .01)	5.37 (p< .01)	6.01 (p< .01)	.078 (NS)	2.39 (p< .05)	1.26 (p< .05)
Word learning cued recall	1.97 (NS)	.63 (NS)	2.96 (p< .01)	1.35 (NS)	4.86 (p< .01)	6.45(p< .01)
ABCD's total recall	.73 (NS)	4.68 (p< .01)	8.66 (p< .01)	3.95 (p< .01))	5.80 (p< .01)	4.05 (p< .01)
Word learning – recognition	3.94 (p< .01)	9.28 (p< .01)	19.97 (p< .01)	6.35 (NS)	18.05 (p< .01)	14.31 (p< .01)
Repetition	5.81 (NS)	5.80 (NS)	20.04 (p< .01)	-.01 (NS)	14.05 (p< .01)	14.23 (p< .01)
Object description	1.40 (NS)	2.33 (p< .01)	3.98 (p< .01)	3.74 (p< .01)	5.32(p< .01)	1.65 (NS)
Read comprehension (words)	2.74 (p< .01)	1.63 (p< .01)	2.99 (p< .01)	.89 (NS)	2.26 (p< .05)	1.54 (p< .05)
Read comprehension (phrases)	.58 (NS)	1.08 (NS)	2.34 (p< .01)	1.16 (NS)	3.01 (p< .01)	1.80 (p< .05)
Generative naming (semantic category)	2.92 (NS)	1.72 (NS)	9.98 (p< .01)	4.63 (NS)	7.07 (p< .01)	3.68 (p< .05)
Conformation naming	.40 (NS)	3.29 (p< .05)	6.78 (p< .05)	3.69 (p< .05)	6.23(p< .05)	-.23 (NS)
Concept definition	.58 (NS)	13.79(p< .01)	24.91 (p< .01)	14.37(p< .01))	24.45 (p< .01)	11.04 (p< .05)
Generative drawing test	.46 (NS)	4.97 (p< .01)	5.16 (p< .01)	5.43 (p< .01)	5.43 (p< .01)	3.92 (p< .01)
Figure copying	.27 (NS)	3.46 (p< .05)	6.34 (p< .05)	3.18 (p< .05)	5.55 (p< .01)	3.21(p< .01)
Story retelling (delayed response)	1.44 (NS)	5.40 (p< .01)	9.46 (p< .01)	3.96 (p< .05)	8.23(p< .01)	5.61(p< .05)

Table 4 ROC analysis between healthy cognitive participants and PD patients for all ABCD subtests

	AUC	SE	p-level	95% CI
Mental status	.411	.071	.255	.271-.551
Story retelling (immediate)	.593	.083	.236	.431-.755
Following commands	.956	.035	.000	.887-1.00
Comparative questions	.663	.080	.037	.506-.820
Word learning (controlled encoding)	.715	.067	.006	.584-.845
Word learning – free recall	.736	.067	.003	.604-.867
Word learning cued recall	.556	.079	.477	.401-.710
ABCD's total recall	.572	.078	.355	.420-.725
Word learning – recognition	.731	.066	.003	.601-.860
Repetition	.511	.079	.892	.356-.665
Object description	.475	.082	.749	.314-.636
Reading comprehension (words)	.722	.079	.004	.568-.876
Reading comprehension (phrases)	.590	.077	.250	.440-.740
Generative naming (semantic category)	.617	.078	.135	.463-.770
Conformation naming	.539	.078	.618	.385-.693
Concept definition	.621	.085	.122	.454-.788
Generative drawing test	.509	.079	.910	.354-.664
Figure copying	.589	.081	.255	.429-.748
Story retelling (delayed response)	.492	.088	.920	.320-.664

Table 5 ROC analysis between healthy cognitive participants and PD patients for ABCD constructs

	AUC	SE	p-level	95% CI
Mental status	.589	.071	.255	.449-.729
Episodic memory	.567	.086	.236	.431-.755
Linguistic expression	.762	.065	.000	.634-.889
Linguistic comprehension	.485	.071	.037	.345-.625
Visuospatial construction	.594	.082	.006	.434-.755
ABCD total score	.675	.081	.003	.516-.835

Table 6 ROC analysis between PD and PDD patients for all ABCD subtests

	AUC	SE	*p*-level	95% CI
Mental status	.753	.075	.005	.607-.900
Story retelling (immediate)	.803	.072	.001	.661-.945
Following commands	.433	.089	.461	.258-.608
Comparative questions	.696	.084	.032	.531-.860
Word learning (controlled encoding)	.840	.064	.000	.715-.965
Word learning – free recall	.684	.082	.043	.524-.845
Word learning cued recall	.776	.079	.005	.611-.903
ABCD's total recall	.808	.070	.001	.671-.945
Word learning – recognition	.809	.071	.001	.669-.949
Repetition	.667	.083	.067	.504-.829
Object description	.810	.068	.001	.677-.944
Reading comprehension (words)	.669	.081	.029	.541-.857
Reading comprehension (phrases)	.806	.067	.001	.675-.936
Generative naming (semantic category)	.823	.063	.000	.698-.947
Conformation naming	.850	.057	.000	.737-.962
Concept definition	.824	.065	.000	.697-.951
Generative drawing test	.829	.069	.000	.693-.964
Figure copying	.742	.083	.008	.579-.905
Story retelling (delayed response)	.830	.066	.000	.701-.959

Table 7 ROC analysis between PD and PDD patients for ABCD constructs and ABCD total score

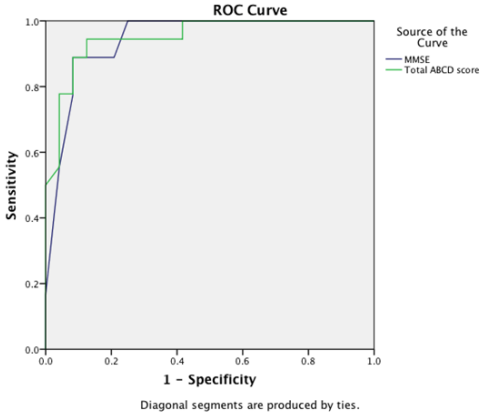
	AUC	SE	*p*-level	95% CI
Mental status	.753	.075	.005	.607-.900
Episodic memory	.801	.068	.001	.668-.934
Linguistic expression	.954	.031	.000	.893-1.00
Linguistic comprehension	.916	.048	.000	.822-1.00
Visuospatial construction	.812	.076	.001	.664-.961
ABCD total score	.950	.032	.000	.888-1.00

Moreover, ROC analysis between PD and PDD patients revealed that thirteen ABCD subtests out of nineteen, showed significant positive effect sizes. These included the computed story retelling (immediate)(AUC .803, p= .01), word learning (controlled encoding)(AUC .840, p< .01),ABCD's total recall(AUC .808, p< .01),word learning – recognition(AUC .809, p< .01),object description(AUC .810, p< .01),read comprehension (phrases)(AUC .806, p< .01),generative naming (semantic category) (AUC .823, p< .01),conformation naming(AUC .850, p< .01),concept definition(AUC .824, p< .01),generative drawing test(AUC .829, p< .01),story retelling (delayed response)(AUC .830, p< .01). A medium effect was noted for mental status(AUC .736, p< .05) and word learning cued recall(AUC .776, p< .05).The remaining subtests showed non significant and low effect sizes i.e. Following commands(AUC .433, NS), Comparative questions(AUC .696, NS), Word learning – free recall(AUC .684, NS), Repetition(AUC .667, NS), Read comprehension (words)(AUC .669, NS), Figure copying(AUC .742, NS) (Table 6).

A significant high effect was also noted between PD and PDD patients, in all ABCD constructs: episodic memory (AUC .801, p= .01), linguistic expression (AUC .954, p< .01) linguistic comprehension (AUC .916, p< .01), Visuospatial construction (AUC .812, p= .01), ABCD total score (AUC .950, p< .01), and a medium effect on mental status (AUC .753, p< .05) (Table 7).

Furthermore, an ROC analysis revealed that the ABCD total score had slightly better discriminatory power in detecting cognitive declination in PD, with an AUC of .950, p < .01 compared to the MMSE, AUC .943, p < .01(Figure 1).

Figure1. ROC curve for cognitive declination in PD between ABCD and MMSE



Discussion

In this study we compared the cognitive and language performance of patients with PD, PDD, AD, and cognitive healthy participants. We found cognitive deficits in all patients' subgroups with the AD group showing the worse overall performance. It was expected that our PD patients would perform differently on the ABCD battery compared to the PDD and AD patients. Early stage PD patients had mainly executive function deficits (following commands subtest) compared to the healthy group. This type of deficit has been reported in approximately 30% of non-demented PD patients [44]. Further, the PD group had evident memory and language disturbances. Studies have reported that memory impairment in PD is variable and that performance is typical of a subcortical pattern of performance potentially arising from executive dysfunction, and others showing rapid forgetting and poor recognition memory, a pattern much more often associated with cortical dementias such as AD [45]. Furthermore, our findings provide evidence that even early PD patients, have cognitive impairment [12, 46-47].

Several studies have provided evidence of cognitive impairment in over 20% of PD patients at the time of diagnosis [44,47]. Aarsland, et al. [4] reported that over 80% of PD patients will develop dementia over an 8 year period, while others suggest that cognitive impairment may be predictive in developing dementia later [48]. Several reports [22-23, 49-51] have noted that verbal learning and recall/retrieval tasks are declined even in the earliest stages of PD, without broad cognitive deterioration or dementia. Our results are in line with the above findings. These tasks were also found to be correlated with plasma concentrations of dopamine for on and off stages [52]. Others have underlined the positive or negative impact of dopamine on cognitive performances in PD [53-54] and in the future research findings from the ABCD can be correlated with such studies. In contrast Jellinger (2012) [55] suggested that cognitive impairment was the result of heterogeneous mechanisms rather than a main neurochemical impairment.

Studies that investigated reading comprehension in early stage PD patients without dementia found that these difficulties were most closely related to memory, high-level language, and PD symptom severity status [56]. Generally PD patients, even those in the early stages who do not have onset of dementia, can experience language comprehension difficulties, particularly when faced with processing more complex stimuli linked to the cognitive status of the individual with PD [50, 57-58]. This finding is in keeping with this study, and denotes that the ABCD

battery can contribute towards the diagnoses of cognitive impairment in non-demented PD patients.

In contrast to previous research in non-demented PD patients [23, 59] which found that memory impairment is more common early in the course of cognitive decline, we found that impairment in recognition is nearly as common as in free recall and confirm earlier studies that noted similar results [21, 23]. This finding is different from what is commonly reported, where deficits occur in both encoding and retrieval in PD [45]. At this point it should be noted that AD-type pathology is common in PD; in an earlier study, amyloid deposition was found in up to 100% of PDD patients and 50% of the PD patients without dementia [60].

Although it is difficult to discriminate between PD and PDD in general, the ABCD battery appears to provide support in this regard. From our findings, it is clear that an in depth neuropsychological and speech and language assessment must be done which may assist in diagnosis, even in the earliest stages of PD or in patients without broad cognitive deterioration or dementia. The above is also noted in research that examined cognitive skills such as working memory [58, 61-65] visuospatial perception and construction [51, 60, 66-70] or attention, particularly visual attention and processing speed [50, 51, 57, 62, 71-75]. What researchers have generally suggested is the importance of creating a valid test that would provide cut-off scores for PD prevalence and distribution between subtypes. Pfeiffer et al. (2014) [27] provides such evidence and in keeping with our findings the ABCD can be utilized in this respect. Studies have also reported that verbal memory and executive function assessments are predictive of PDD, whereas other studies supported that visuospatial disability is predictive for PDD [14, 18, 76-78]. We found that the ABCD visuospatial and naming tests showed more marked dysfunction for the PDD patients than those of the PD patients. Regarding the memory domains previous research has shown that verbal memory impairment is an early cognitive deficit and visual memory impairment is common in PDD patients [9, 18, 78-79].

Moreover, research has noted that it is difficult to discriminate between PDD and AD using neuropsychological tests only, particularly at the early stages [22-23, 26] and sometimes PDD is often misdiagnosed and confused with mild AD [73]. This research suggests that the ABCD may assist in this respect. It is essential that clinicians routinely screen cognitive impairment in early PD, since Litvan et al. (2011) [12] reports prevalence of cognitive decline in 38.2% of cases. Other studies reported evidence of cognitive impairment on neuropsychological testing in over 20% of PD patients at the time of diagnosis [44, 47] and over 80% of PD patients will develop dementia over an 8 year period [4, 20]. Research further suggests that comprehensive neuropsychological evaluations of multiple domains including episodic memory, executive function, attention, visuospatial function and psychomotor speed [21, 27, 47, 72, 80, 81, 75-86] have found data consistent with our findings for the ABCD. Several limitations however restrict the generalisability of our findings. These include the relatively small sample size of the patient groups, because of the strict exclusion criteria. Further research with additional analyses is required in order to confirm the findings of this study in larger samples. Furthermore, we did not compare our findings to an established comprehensive neuropsychological battery that could be considered the "Gold Standard" for discriminating the clinical groups. However, despite these limitations, we were able to establish the usefulness of the ABCD as a cognitive screening battery in patients with PD, PDD, and AD.

Conclusions

In conclusion, this research suggests that the occurrence of cognitive impairment in patients with PD is noted even in the early stages of the disease. The combination of neuroimaging and in depth assessment of neuropsychiatric, neuropsychological and language symptoms in PDD and AD can lead to more accurate discrimination between the two, and the ABCD has the potential to assist in this respect. It is further suggested that several ABCD subtests can assist in the early prognosis for onset of dementia in PD.

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Application of the diagnostic tool EFA-4 in dementia

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Abstract

Speech is a brain function that includes virtual, mobile and sensory part for the understanding and the production of spoken and written language. The aim of this study was to present the adaptation of the diagnostic tool Examining for aphasia – 4th edition (EFA -4) in the Greek language. In dementia and especially in Alzheimer's disease (AD), the speech and language disorders are the main diagnostic features, along with the worsening impairment of memory. The diagnostic tool EFA-4 is a standardized, reliable and valid measure of speech and language disorders. The test was administered to 50 adults separately. The sample selection, although it had uniformity in age, was regardless of origin, marital status and socioeconomic status. According to the results of the research, the EFA-4 is perceived to be particularly useful in the setting of language deficits of the patients with AD, who participated in the survey.

Introduction

The specific scientific term aphasia refers to any loss, partial or total, of language ability in children and adults, as well as to any general speech impairment after a normal brain establishment. Aphasia is defined as the acquired disorder of language understanding, production and symbolic knowledge [1]. In the case of aphasia the patient cannot speak, apply the correct meaning to words, understand speech and at times cannot write or read. Every aphasic disorder is different and unique and is morphologically affected depending on the locus, the severity and the starting point of the disfunction. Aphasia comes as a result of a brain damage (AEE, head injury). However, it has been proven that speech disorders and particularly aphasia are a common phenomenon of neurodegenerative diseases.

Speech disorders – Aphasia and Alzheimer's (AD)

Scientific research has shown a great interest in speech disorders, aphasia, dementia and more particularly AD. It has been scientifically documented that aphasia is present in all kinds of dementia and is one of the diagnostic criteria [2,3,4]. Specifically, the first Alzheimer's patient was aphasic [5]. However, only recently has aphasia been acknowledged as a major feature of AD. AD is the most common type of dementia, representing the 2/3 of all dementias. In the past years it was considered relatively rare and specific to people under 65 years of age. In the first half of the 20th century there were only 100 AD cases noted. Nowadays we are aware of the exact opposite: the disease is extremely common, especially in developed countries, while there is an exponential growth in its frequency as people get older. Age is the most important danger factor for the application of the disease. Between the ages of 65 and 85 the prevalence of the disease is constantly increasing, reaching at the age of 85 a striking 35-40%. AD is not related to the typical aging process and is characterized by a non-typical decline of brain functions; among which speech has a central role. Language deficiencies are obvious from the very early stages of the disease [7]. All AD patients show aphasic speech disorders as dementia progresses [8]. AD speeds up speech decline independently of the patient's age, compared to the decline present in typical aging and mild cognitive impairment – MCI [9]. Moreover, the type of speech impairment in AD is different from that in Vascular Dementias [10,11] or Front Temporal Dementias [12]. The functional use of language, or Pragmatics, contributes to the communicative loss in dementia[13]. There is poor maintenance threads in conversation, there is short but frequent change of subject, request for more instructions, pauses in speech production with many ambiguities, incoherent speech, difficulty in maintaining eye-contact and difficulty in giving turns during a conversation [14,17]. Pragmatic deficiency may depend on the kind of interaction [18]. AD speech is described as lacking coherence [16], deranged and shortened in content [16,19,20], as well as a wide use of vague references[15,16].

Lexical – semantic deficiencies in AD are characterized by a restricted vocabulary use [21] and difficulty in naming [22], which are probably caused by an interruption in cognitive processing, perhaps during the pre-lexical stage. Lexical difficulty is one of the early deficiencies noted in people suffering from dementia [23]. Naming difficulty is the central issue of the many researches concerning speech disorders in dementia [24,25,26,27,28]. The majority of researches seem to support the view that the initial interruption in word recovery is due to a cognitive and not a perceptive deficiency.

Furthermore, syntax remains unaffected in AD, except for the last stage [24,25,29,30,31]. Nevertheless,

there have been reported syntactic errors such as phrase and sentence loss, as well as interruption of phrases and grammatical disagreement [32]. The perception of syntax is relatively more affected than the production [33,34]. One explanation could be that syntax is a relatively automatic cognitive function which remains unaffected during a general cognitive decline [35].

As far as phonology is concerned, phonological decline in AD patients are very rare and present only in the last stages. Even though phonological errors have been reported in some researches, they appear to be a part of a higher semantic or syntactic decline and not an individual decline in verbal sounds or morpho-phonemes (individual linguistic units that signify a change in meaning).

Schematically AD can be divided into three stages. The speech disorders of each stage can be presented as follows. In the first stage of AD, as far as pragmatics is concerned, there is difficulty in the use of naming references, difficulty in coherence, instruction, narration of stories, understanding of humour and sarcasm, there is difficulty in understanding abstract notions, difficulty in starting speech production as well as in retaining the subject of a conversation. Additionally, there is an ambiguous use of language while there need to be repeated clarifications. In semantics there is difficulty in finding the required word and frequent use of periphrasis as well as hand gestures. In syntax and phonology, during this stage, we come up with almost no error. In the second stage of mild AD, there is a poor usage of the naming reference, as far as syntax is concerned, lack of coherence and difficulty in preserving the subject of conversation. There is little use of abstract ideas and frequent repetitions. Speech is largely depended on stereotypic expressions. In Semantics, there is poor word flow with a limited vocabulary and increased use of periphrasis and failing replacements. There is frequent use of empty speech. In Syntax there are occasional grammatical errors and difficulty in understanding complex structures. In phonology there are generally no errors at all. In the third, also known as late, stage of AD there is lack of coherence, difficulty in maintaining eye contact, expression of irrelevant ideas, persistence, irrational speech and even silence. In Semantics there has been observed paraphasia, echolalia, extremely poor understanding, severely weakened naming ability, frequent ideoglossia and incomprehensible speech. In Syntax, while grammar remains generally unaffected, there is a fragmented use of incomplete sentences and phrases, as well as a poor understanding of grammatical structures. In the late stage phonological errors are more common.

It is therefore made clear that speech disorders are part of each of the three stages. Despite the universality of aphasia, in dementia the qualitative substance as well as its severity vary depending on the pathological process and its detection [6]. It is the duty of health professionals to do an initial correct diagnosis and then create a complete treatment plan. What we should keep in mind is that the more accurate the diagnosis is the more effective will the treatment be.

Diagnosis

The existence of dementia must be attested by a clinical examination – application of criteria DSM-IV, NINCDS-ADRDA – and the stage of the disease must be confirmed with the Mini-Mental State Examination (MMSE). During the paraclinic control, along with the blood and biochemic routine tests, there also needs to be a measuring of Vitamin B12 level and of the Thyroid hormones [36,37]. In our effort to improve the diagnosis and to better specify the patients' speech difficulties we translated and adapted the diagnostic testing EFA-4 (Examining for Aphasia) into the Greek language.

Purpose

The aim of our research was to manage to give another diagnostic look for Dementias. The diagnostic approach should be characterized by reliability and validity, including new measurement methods of aphasia. Our purpose as therapists is to be able to rely on the results of our measurements in order to improve the therapeutic processes for these people. This improvement will help us improve the daily lives of patients with dementia.

Materials and Methods

What is EFA-4 diagnostic testing

EFA-4 is a regulatory, reliable and valid measuring of aphasia. It is suitable for adults whose language functions weakened after a normal establishment of language. EFA-4 offers to the clinic a method for evaluating possible aphasic linguistic deficiencies and other acquired disorders which are usually closely related to language functions. It also allows the examiner to find out about the individual's participation in activities that might have been amended by aphasia.

EFA -4 Subtests

EFA-4 includes 10 subtests which have been created in order to evaluate the basic brain functions. Those subtests include visual recognition, acoustic recognition, tactile sensing, the acoustic comprehension of oral speech and the silent recognition with understanding. Additionally, verbal as well as non-verbal behaviour is tested, meaningful speech production and meaningful writing ability. Finally, we evaluate communicative and descriptive speech.

The parts of EFA-4

EFA-4 consists of the examiner's manual, a book of images, a results record sheet – diagnostic form, an answer

sheet – short test form, a brief diagnostic sheet, a form of personal medical records and an object box. *In the research conducted we used the results record sheet – the diagnostic form, the results record form and the object box.*

The use of EFA-4

EFA-4 is a well structured tool with excellent psychometric properties. It has five main uses: (a) to detect the existence of aphasia, (b) to define the severity of aphasic signs and symptoms and their effect on life participation and activities, (c) to set goals for the rehabilitation of communication, (d) to record the progress made during the treatment, and (e) to inform and consult patients of aphasia, their families and the supporting social network, as well as to inform the doctors, the medical staff and Insurance Funds.

Scoring of the testing

The activities are scored with 2, 1, or 0. The main parameters of the test taker's answers that should be taken into account during the scoring are accuracy, consistency and effectiveness. An activity should be scored with a 2 for an answer that is correct, direct and effectively produced as well as when the test taker indicates or writes correctly as required.

- Scoring 1 should be given for an answer that is correct but according to the examiner is delayed or inefficiently produced (usually due to non-standard, unsteady or poorly coordinated verbal or writing movements). Scoring 1 should also be given when an answer itself is correct, but the form of the answer is not correct (i.e. a written answer to an oral question).
- Scoring 0 should be given if the test taker does not respond to the activity at all, or answers incorrectly. The examiner should indicate the cases where there is no answer by writing down N/A (No Answer) next to the activity along with 0.

The scoring of answers in EFA-4 activities requires a careful observation of the behaviours and clinical judgement.

Methodology

Research design

The research was divided into four parts. We began with the translation of both examinations in Greek. Then we did a pilot research to check the adaptations to the Greek language. The third part consists of the administration of the test, the coding data and the introduction of the data. The fourth part is about the analysis of the data and the interpretation of the results.

Translations and adaptation of the axamination

The translation of EFA-4 from English into Greek was done in the following procedure: the original versions of the examination were translated independently by three native speakers of Greek who were efficient in both written and spoken English. The three Greek versions were again translated into English by three different native speakers of English who were efficient in written and spoken Greek. From the three translations, the stimulus – images that were accurately translated from English into Greek and vice versa – were included in the final versions of the examination. Furthermore, the three Greek versions were given to three bilingual (English-Greek) judges, along with the English versions, in order to attest the final outcome. Finally, two speech therapists and a linguist – who edited the changes in both linguistic and lexical level – were chosen to check whether the adaptations were adequate and they attested the final Greek version.

Pilot research

The pilot research was conducted from July 2010 to January 2011 in order to define the difficulty of the objects and to verify their accuracy and other characteristics.

Sample

In the current research the examination was administered to 100 adults separately (50 with AD and 50 as control group). The sample selection, although it had uniformity in age, was regardless of origin, marital status and socioeconomic status. It should be noted that in order to successfully administrate the scale and measurements we had to reassure the participants that their personal data would remain confidential and that they would have to sign a participation letter.

Data collection

The administration of the examination took place at the Outpatient Department of the C' Neurologic Clinic of G.H. Papanikolaou, in the presence of the patients and their caregiver. After the introductions with the test takers we proceeded to the explanation of the purpose of the examination and we asked for their consent by signing the participation letter. Afterwards the test takers were seated in front of a table across and slightly to the right of the examiner. The lighting conditions were appropriate and the materials were placed in such a way that the patients could see and use them without difficulty. The examination was distributed to all participants under the same procedure, and it followed the instructions found in the administrative manual.

During the evaluation the examiner did not change their facial expression or express verbal disapproval. However, in order to obtain the highest performance on the part of the test takers, the examiners tried to encourage them. They were supportive but objective. They would tell the participants when they did well and they calmed them down when they failed. According to Schuell (1964), a simple and honest way to do that, is to comment on reality when the test taker faces a difficulty with a task. This will help the patient relax, get back on track and clear his mind in order to proceed. This is what each examiner should learn. This is not an easy work nor does it aim to simply collect random numbers. The aim is to have the best possible cooperation between the patient and the examiner. There should be successful communication, always with a smile and discussion. The duration of the examination varies from participant to participant but the average is between 45 to 60 minutes.

Results

Standardness or nonstandardness control of the observations' distribution for the whole sample as well as the subgroups was done using the Kolmogorov – Smirnov method. The Standardness control showed that our sample had a standard distribution. An independent sample t-test was conducted in order to see whether there is a statistically significant difference between standard witnesses and dementia patients. The analysis gave us the following Table 1.

Table 1: Comparison of the answers according in terms of pathology for all subtests of EFA – 4

100	Control Group (N= 50) M.O (T.A.)	Dementia Patients (N= 50) M.O (T.A.)	t- value	df	p- level
1. Recognition	109.70 (.707)	76.52 (27.627)	8.490	98	.000
2. Speech Comprehension	98.68 (2.369)	39.92 (18.866)	21.822	98	.000
3. Speech Production	169.28(1.604)	109.35(37.481)	11.297	98	.000
4. Numeric Procedures	19.84 (.468)	6.32 (5.389)	17.674	98	.000
5. Written Language	49.66 (1.010)	17.30 (16.489)	13.825	98	.000
6. MMSE/HINDI	29.62 (1.612)	18.51 (5.370)	14.867	98	.000

According to Table 1, there were statistically significant differences between the two intervals of confidence of the statistical analysis.

In our effort to relate the educational level with pathology separately, in terms of the subtests and MMSE/HINDI scale, we came up with the following Table 2. It shows that answers are affected by educational level, but such relation is not statistically significant. In contrast to pathology and MMSE/HINDI, where the relation presents a statistical significance.

Table 2: Association of answers according to pathology and educational level.

N=100	Educational Level	Pathology	MMSE/HINDI
	r (p- level)	r (p- level)	r (p- level)
1. Recognition	-.016 (.01)	-.651 (.01)	.841 (.01)
2. Speech Comprehension	-.032 (.01)	-.911 (.01)	.949 (.01)
3. Speech Production	-.027 (.01)	-.754 (.01)	.924 (.01)
4. Numeric Procedures	-.089 (.01)	-.871 (.01)	.930 (.01)
5. Written Language	-.189 (.01)	-.813 (.01)	.871 (.01)
6. MMSE/HINDI	-.053 (.01)	-.842 (.01)	-----

In trying to examine whether the stimuli for every scale axis separately affect the final performance, we created a multiple linear model for all stimuli. From the statistical analysis for the pathological sample we came up with Table 3. Whether the selection of stimuli affects the parameter of the test that explains the existence of a satisfactory level of promptiness,Table 3 gave us statistically significant effects for every scale axis separately, but further improvements are possible.

Table 3: Results of the linear model for all stimuli in relation to the general performance EFA – 4 .

N=100	R^2	p- level
1. Recognition	1.000	.000
2. Speech Comprehension	1.000	.000
3. Speech Production	.898	.000
4. Numeric Procedures	1.000	.000
5. Written Language	1.000	.000

In order to check the predictive accuracy we used the application of the paired sampled t-test, on the basis of pathology –with which we evaluated the performances for every test thematic – and we examined the possibilities of rejection or verification of our zero hypothesis. The results are summarized in Tables 4 and 5.

Table 4: Predictive acuuracy check for the scale and mmse/hindi

	Paired test	Paired test
1. Recognition	-.651	.000
2. Speech Comprehension	-.911	.000
3. Speech Production	-.754	.000
4. Numeric Procedures	-.872	.000
5. Written Language	-.813	.000
6. MMSE/HINDI	-.842	.000

Table 5: Paired test results

	Paired test	p-level
1. Recognition	-91.610 (25.943)	.000
2. Speech Comprehension	-67.800 (32.875)	.000
3. Speech Production	-138.121 (40.336)	.000
4. Numeric Procedures	-11.580 (8.229)	.000
5. Written Language	-31.950 (20.374)	.000
6. MMSE/HINDI	-23.052 (7.343)	.000

According to the Table above, there are satisfactory levels of accuracy and unequivocal differences on the basis of pathology. Finally, for the structural validity (or validity of the notional structure) and reliability control, we created the reliability indicator of internal validity – relevance of the thematic indicators alpha Cronbach, split half, and Kuder – Richardson. These results are summarized in Table 6. As far as the internal relevance control or the uniformity of the scale stimuli are concerned, we calculated the alpha Cronbach's factor. The analysis provided us with the following:

Reliability Coefficients 5 items Alpha = .924 N of Cases = 100

Reliability Statistics			
Cronbach's Alpha	Part 1	Value	,942
		N of Items	3[a]
	Part 2	Value	,772
		N of Items	2[b]
		Total N of Items	5
		Correlation Between Forms	,927
Spearman-Brown Coefficient		Equal Length	,962
		Unequal Length	,964
		Guttman Split-Half Coefficient	,663

a. The items are: Recognition, Speech Comprehension, Speech Production.

b. The items are: Speech Production, Numeric Procedures, Written Language

Another method has to do with internal relevance control or uniformity about scale stimuli the coefficient alpha Cronbach's splits in half. From this analysis we came up with the following (Table 6):

Table 6: Validity and reliability control for the scale EFA - 4 (Kuder – Richardson)

Lambda	Kuder – Richardson
1. Recognition	.956
2. Speech Comprehension	.924
3. Speech production	.663
4. Numeric Procedures	.973
5. Written Language	.973

As you can see, the above Table presents satisfactory validity and reliability levels.

Discussion

The aim of this research was the pilot application of EFA-4 in Greek language to dementia patients. Additionally, our aim was to test whether the selected stimuli can lead to a possible diagnosis of the existence of speech disorders in dementia, as well as the validity and reliability control of the specific test. The results of the research are summarized in the following list:

1. There is a statistically significant difference between the average rate of answers of the control group and the dementia patients, for all EFA-4 axis.
2. There is a statistically significant difference between the average rate of answers between the average rate of answers of the control group and the dementia patients, for MMSE/HINDI.

3. To the question whether educational level affects performance for EFA-4 axis, there was a statistically insignificant inverse correlation effect (due to low educational level of the sample).
4. To the question as to whether pathology affects performance for the EFA-4 axis there was a statistically significant inverse correlation effect (that is, the more advanced the stage is the less effective the performance is for all axis of the test). This effect varied from 65,1% for reading and 91,1% for comprehension.
5. To the question whether there is a relation between MMSE/HINDI scale and EFA-4 axis, the answer is that there is a statistically significant proportional relationship, with a positive correlation of 84,1% for reading and 94,9% for comprehension.
6. As to whether each stimulus separately can -and to what extend- explain the level of each EFA-4 axis, the research showed that they can actually be explained to a high or even absolute degree.
7. To the question whether we have a reliable scale – measuring tool, the research showed that the current form of the scale is actually a highly reliable tool.
8. Finally, to the question whether we have a valid scale – measuring tool, the research showed that for the specific age group the scale is considered a valid tool.

The authors declare that they have no conflicts of interest.

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Cerebrospinal fluid alpha-Synuclein levels in patients with Parkinson Disease, multiple system atrophy and healthy controls

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Abstract

Diagnosis and especially differential diagnosis among synucleinopathies, such as Parkinson's disease (PD) and Multiple System Atrophy (MSA) is difficult, especially at the early stages, rendering the use of one or more biomarkers very much needed. The aim of the present study was to examine the utility of cerebrospinal fluid (CSF) alpha-synuclein (α-Syn) levels, an emerging new biomarker, in patients with PD and MSA vs. healthy controls (CTRL). A total of 54 patients were included in the study, divided into 3 groups of comparable age and sex: 18 PD, 11 MSA and 23 CTRL. Clinical diagnoses were made according to internationally established criteria and CSF α-Syn levels were measured by an in house sensitive ELISA method. CSF samples with >50/μl erythrocytes were rejected. In PD α-Syn levels were significantly decreased compared to the CTRL group ($P<0.01$), while in MSA they were significantly higher as compared to CTRL and PD ($P<0.05$ and 0.001 respectively). No significant correlations were found between CSF α-Syn levels and age, gender and disease duration. To our knowledge, this is the first study reporting an increase in CSF total α-Syn concentration in MSA, suggesting α-Syn as a surrogate marker for MSA. This finding may be compatible with increased tissue levels of α-Syn in MSA brain, as previously reported.

Introduction

Early diagnosis of neurodegenerative disorders is difficult, especially at the early stage. However, it is considered necessary for a number of reasons, mainly for accurate prognosis and proper treatment [1]. Cerebrospinal fluid (CSF) biomarkers can be a good tool for early diagnosis, since CSF directly interacts with the extracellular space of the brain and mirrors biochemical alterations occurring in it [2]. In Alzheimer's disease (AD), the most common neurodegenerative disorder, CSF biomarkers [namely total Tau, phosphorylated Tau and β-amyloid peptide (Aβ42)] have been widely recognized as valuable tools in diagnosis [3,4]. Recently, the new diagnostic criteria for AD, established by the National Institute on Aging and the Alzheimer's Association (NIA-AA) recommend the use of the above mentioned biomarkers to increase confidence that the underlying dementia syndrome is due to an AD pathophysiological process [5].

Parkinsonian syndromes are mainly neurodegenerative in nature, with Parkinson's disease (PD) being the most common disorder. Among other forms of parkinsonism, multiple system atrophy (MSA) is commonly misdiagnosed on clinical grounds [6, 7]. The pathologic hallmark of PD is the eosinophilic intraneuronal inclusions, the Lewy bodies, the main component of which is the protein alpha-synuclein (α-Syn) [8, 9]. MSA is characterized by glial cytoplasmic inclusions, also containing α-Syn, both diseases belonging to the group of "synucleinopathies" [10]. The clinical diagnosis of PD and its differential diagnosis from MSA are not always easy. Recent evidence suggested the quantification of α-Syn in CSF as a candidate biomarker for synucleinopathies [11]. However, despite the growing body of research, the potential use of α-Syn as a CSF biomarker for the differentiation among synucleinopathies has been limited. Several studies measuring CSF α-Syn levels in Parkinson's disease and MSA have yielded conflicting results [12-28]. The disparity among these studies probably resulted from methodological issues, including variation in antibodies that might detect different species of α-Syn, a less than rigorous quantitative method, limited numbers of patients in some investigations, or inadequate control for important confounding factors, particularly blood contamination in CSF.

The aim of the present study was to examine the utility of quantification of CSFα-Syn in order to differentiate patients with PD, MSA and CTRL, after strict control of many confounders in the CSF.

Subjects, Material – Methods

Patients

Patients and controls were consecutively and prospectively recruited (between 2011 and 2014), without selection, through a routine process. The study was performed according to the ethical guidelines of the 1964 Declaration of

Helsinki and had the approval of the local committee of our hospital.

A total of 54 patients were included in the study, divided into 3 well characterized groups: (a) The PD group comprised 18 patients, fulfilling the UK Parkinson's Disease Society Brain Bank Criteria for the Diagnosis of PD [29]. b) The MSA group comprised 11 patients fulfilling, the Second consensus statement on the diagnosis of multiple system atrophy diagnostic criteria [30]. c) The control group (CTRL) comprised 23 otherwise normal individuals with comparable age that had undergone minor surgery (such as hernia repair or knee joint surgery) under spinal anesthesia.

All patients underwent a detailed evaluation (medical history, physical and neurological examination, blood tests to exclude metabolic causes of Parkinsonism, MRI and DaTScan (only for MSA patients). Laboratory evaluation included complete blood count; serum electrolytes, blood urea nitrogen, creatinine, glucose, vitamin B12 and thyroid stimulating hormone; all results being within normal limits. No patient was demented, as assessed by the Mini Mental State Examination (MMSE) and the Frontal Assesment Batery (FAB). Additionally, they all were followed up for at least 2 years in an effort to ensure correct diagnosis and doubtful cases were rejected. Demographic data for patients and controls are listed in table 1.

Sample collection and biochemical determination

Lumbar puncture was performed after informed consent or for routine diagnostic purposes at the L5-S1 interspace, between 9-10 AM after overnight fasting. Samples were obtained in polypropylene tubes. Up to 15 ml CSF was taken from each subject, with every 5ml pooled into one fraction. They were immediately centrifuged (2000 rpm×10min) for removal of cells, aliquoted (0.5-0.75ml) into polypropylene tubes and stored at -80˚C until analysis; they were thawed only once, just before the assay. To avoid any potential variations arising from a rostro-caudal gradient, the same fractions of both patients and the control group 8th-10th ml were assessed. Samples with more than 50 red blood cells (RBCs) were rejected.

Standards and CSF samples were measured in triplicate, by an in house double sandwich enzyme-linked immunosorbent assay (ELISA), according tothe method previously described [31]. In brief for α-Syn determination, two commercially available α-Syn-specific antibodies were used: the monoclonal Syn-1 (BD Transductions) as capture antibody and the polyclonal C-20 (Santa Cruz) as detection antibody, after its covalent conjugation with HRP. Each ELISA plate (Corning Costar) was coated for 24 hrs at room temperature with 0.5 μg/ml of Syn-1 antibody (50 μl per well) in 100 mM NaHCO3, pH 9.3. The plates were washed three times in wash buffer (50 mMTris-HCl, 150 mMNaCl and 0.04% Tween-20) and recombinant human α-Syn (Chemicon) (as standard) appropriately diluted in TBST/BSA (10 mMTris-Cl, pH 7.6, 100 mMNaCl, 0.1% Tween-20 and 1% BSA) or 45 μl of CSF sample mixed with 5 μl 10x TBST was added. To allow antigen binding, plates were incubated at 37oC for 2.5 hrs. After washing three times with wash buffer, 50 μl of HRP-conjugated C-20 antibody (4000x diluted in TBST/BSA) were added to each well and further incubated for 1 hr at ambient temperature. The wells were washed and 50 μl of chemiluminogenic HRP substrate (UptiLight HS ELISA HRP substrate, Interchim) were added to each well. Following incubation for 10 min at ambient temperature, chemiluminescence was integrated for 1 s.

Statistical analysis

All variables were checked for normality and homogeneity of variances by the Shapiro-Wilk's and Leven's tests respectively. Levels of CSF α-syn showed deviations from normality and their variances were heterogeneous. Logarithmic transformation restored these violations and permitted the use of 2-way analysis of covariance (ANCOVA), with diagnostic group and sex as cofactors and age as a covariate. One-way analysis of variance (ANOVA), t-test, Kruskal-Wallis test, Spearman correlation coefficient and χ^2 test were also used as appropriate.

Results

Biochemical data are shown in Table 1. The studied groups did not differ among each other in respect to age and sex. As expected, patients with MSA had shorter disease duration as compared to PD. Since CSF α-Syn levels did not follow the normal distribution, data are presented as median values (25th-75th percentile), but for compatibility with biomarker databases they are also presented as mean ± SD. Comparison with 2-way ANCOVA revealed a significant effect by group, but not by sex, while age did not affect the model significantly. Post-hoc tests revealed that PD presented with lower α-Syn levels as compared to the CTRL group, whilst MSA presented with significantly higher levels as compared to CTRL and PD.

Age and disease duration did not correlate significantly with α-Syn levels in any of the studied groups

Discussion

In the current study we assessed the utility of CSF levels of α-Syn in discriminating PD and MSA patients from controls. CSF α-Syn levels were significantly lower in PD, while in MSA they were significantly higher, as compared to both CTRL and PD groups. No significant effect of age, sex and disease duration on α-Syn levels were observed in CTRL or in the patient groups. Other authors have reported a decrease CSF α-Syn levels with age [15]. Of note, we included a healthy control group, whereas in previous studies the control group comprised of patients suffering from other neurological diseases.

Given the significant role of alpha-synuclein in the pathogenesis of synucleinopathies, it has gained attention as an attractive candidate biomarker for these diseases. Although first believed to exist as an intracellular protein, studies have shown that it is detectable and in the extracellular fluids, such as CSF and plasma, secreted by an exosomal, calcium-depentent mechanism [32]. Data from α-Syn measurements in peripheral fluids (total, oligomeric, phoshorylated) have been inconsistent and, overall, peripheral α-Syn levels despite the ease of sampling, do not appear to have potential as a biomarker [33].

Since CSF is in direct contact with brain parenchyma, a number of studies have attempted to quantify CSF α-Syn. In PD most studies appear to show a reduction of CSF total α-Syn levels patients as compared with controls [12, 13, 15, 17, 19, 24] while, others showed no difference [14, 16, 21, 25-28]. As regards MSA the few studies report either decrease [19, 20, 22, 23, 28] or no change [18, 21]. These inconsistencies have been attributed mainly to methodological factors, involving both pre-analytical and analytical confounders, while differences in the ELISA method used and/or ethnic differences cannot be excluded. All studies are summarized in Table 2.

In the present study, we focused to eliminate such confounders, according to the suggestions of very recent recommendations [34]. Thus, diurnal variation was avoided by performing lumbar puncture in the morning. Food intake was controlled, since samples were collected following overnight fasting. Possible concentration gradient was avoided by measuring the same CSF fraction, while other processing details included use of polypropylene tubes to minimize possible tube-wall absorbance, filling of the tube by the same amount of CSF (3/4 in 1ml tubes) to restrict evaporation and immediate sample processing. Most attention, however was given in blood contamination of CSF, since it has been recognized as the main confounder in CSF α-Syn quantification studies. A-Syn is highly abundant in blood cells, especially in erythrocytes, thus traumatic blood contamination of CSF, which occurs in 10-20% of routine lumbar punctures, should produce false positive results (Mollenhauer et al. 2010, 2011). We have previously shown, that only with <50 RBCs/μl the correlation between RBCs and α-Syn is lost [35]. As regards our optimized ELISA, it has high sensitivity and selectivity. Importantly, the antibodies utilized by this method (Syn1 and C-20) are both commercially available, with well characterized, known epitopes, which ensure recognition of the total levels of the protein, oligomeric and monomeric [35].

Our results of lower CSF α-Syn levels in PD are in agreement with the general trend of lower CSF α-Syn levels in this disorder [12, 13, 15, 17, 19, 24]. On the contrary, this is the first study reporting an increase in CSF total α-Syn concentration in MSA. This finding is compatible with increased tissue levels of α-Syn in MSA brain, previously reported [36]. Additionally, in a post-mortem study, ventricular α-Syn levels were increased in MSA, distinguishing this disorder from other synucleinopathies [37]. However, *in vivo* studies reporting a decrease in CSF α-Syn levels are not characterized by adequate blood control, including more the 50 RBCs in the sample (Table 2).

The present study has certain limitations, namely the small sample size and the lack of *neuropathological confirmation.* However, this is an inherent restriction of the vast majority of studies on biomarkers. To reduce incorrect classification as much as possible, strict application of current clinical criteria, extensive investigation, plus two years follow up were applied.

Table 1. Demographic and biochemical data of studied groups

	CTRL	PD	MSA	*P* values
(males/females)	22 (11/11)	18 (10/8)	10 (6/4)	NS[d]
Age (years)[a]	70.5 ± 7.5	65.0 ± 12.1	69.0 ± 9.2	NS[e]
Disease duration (years)[a]	NA	5.0 ± 2.8	2.5 ± 2.1	0.02[f]
CSF RBCs (/μl)[b]	0 (0-0)	0 (0-7)	0 (0-11)	NS[g]
CSF α-Syn (pg/ml)[c]	99 (81 - 119) 111.4 ± 45.9	65 (59 - 77)* 73.3 ± 26.8	159 (143 - 190)** 178.9 ± 96.2	< 0.0001[h]

CTRL: Control group, PD: Parkinson disease, MSA: Multiple system atrophy,
NS: non-significant, NA: non-applicable. [a] mean ± SD, [b]median (range) [c]median (25th - 75th percentile and mean ± SD, [d]χ^2 test, [e] 1-way ANOVA, [f] t-test,[g]Kruskal-Wallis test, [h] 2-way ANCOVA after logarithmic transformation of original data, followed by Newman-Keuls post-hoc tests.*$P<$ 0.01 vs CTRL. **$P<$ 0.05 vs CTRL and < 0.001 vs PD

Figure 1. Scatterplot of CSF alpha-synuclein levels in patients and controls.

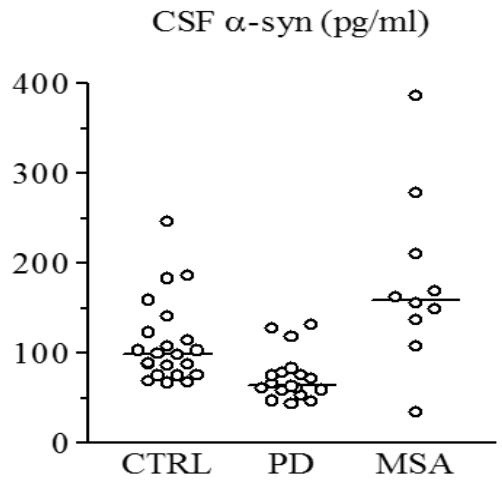

Table 2: A-Syn; Normal values in CSF and statistical differences in PD and MSA patients (in vivo studies)

Ref.	Date	Study	Concentration of CTRL	Units	RBCs control	Hb control	Age of samples	HC n	NC n	ND n	PD (n)	MSA (n)
12	2006	Tokuda et al	~35	ng/ml	—	—	—	9	29		↓ (33)	—
13	2008	Mollenhauer et al	6.0±5.7	pg/µl	—	—	—		13		↓ (8)	—
14	2009	Ohrfelt et al	395(298-452)	pg/ml	<500/µl	—	—		55		→ (15)	—
15	2010	Hong et al	0.47+0.16	ng/ml	—	<200 ng/ml	—	132			↓ (117)	—
16	2010	Reesink et al	18 (14-26)	ng/ml	—	—	—	34			→ (18)	—
17	2011	Parnetti et al	68.9±71.0	ng/ml	<500/mm^3	—	2005-2009		32		↓ (38)	—
18	2011	Shi et al	0.49±0.17	ng/mL	—	<200 ng/ml	—	137			↓ (126)	→ (32)
19	2011	Mollenhauer et al	1.73±1.83 2.22±1.31	pg/µl	<500/µl	—	2003-2006		76 23		↓ (324)	↓ (44)
20	2012	Tateno et al	137.8+31.2	pg/ml	—	—			11		↓ (11)	↓ (11)
21	2012	Aerts et al	25(18-42)	ng/ml	<50/ µl	<0.25µmol/l	—			57	→ (58)	→ (47)
22	2012	Hall et al	67(51-85)	ng/ml	—	<1000 ng/l	—	107			↓ (90)	↓ (48)
23	2012	Wang et al	520±130	pg/mL	—	<200 ng/ml		51			↓ (83)	↓ (14)
24	2013	Wennstrom et al	~700	pg/ml	—	—	—			52	↓ (38)	—
25	2013	Mollenhauer et al	1549+382	pg/ml	<500/µl	—	2009-2011	48			↓ (78)	—
26	2013	Kang et al	40 (12) [36-43]	pg/mL		<200 ng/mL		63			↓ (39)	
27	2014	Parnetti et al	21 (14-43)	ng/mL	—	—	2007-2011		25		↓ (44)	—
28	2015	Magdalinou et al						30			↓ (31)	↓ (31)

HC=Healthy Controls; NC=Neurological Controls; ND=Not Defined n/(n)=number of controls/patients; ↓ = reduced levels; ↑ = increased levels; → = no difference vs. controls; — = not included

In conclusion, despite the aforementioned drawbacks, our results imply that CSF α-Syn may be a promising biomarker to differentiate between PD and MSA. Further studies, using standardized operating procedures, are needed to confirm these findings and extent speculations as to whether combination of α-Syn with other biomarkers may increase the discriminating power.

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The authors declare that they have no conflicts of interest.

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Comparing the latent structure of Raven's educational coloured progressive matrices among young children and older adults: A preliminary study

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Abstract

Objective: The aim of the present study was the comparison of the general cognitive ability (g) between young children and older adults through the investigation of the latent structure qualitative changes in [R] Educational Coloured Progressive Matrices (CPM) from age to age, using Confirmatory Factor Analyses (CFA) and testing a conventional unidimensional model. **Method:** The sample consisted of 42 kindergarten and 56 elementary school students (age range: 5-8 years) and 118 new-old adults and 27 old-old adults (age range: 61-88 years). The participants' cognitive abilities were examined in: (a) the Raven's Educational CPM test, and (b) the Mini-Mental State Examination (MMSE). **Results:** CFA applied to data of the total sample, elementary school students subsample and new-old adults subsample, indicating that individual variability across [R] CPM measured variables (total scores for each of the three sets) can be modeled by one latent variable (a single underlying factor). The same pattern of [R] CPM latent structure was not verified for the subsamples of kindergarten students and old-old adults, since the variance of a single underlying factor was not found to be statistically significant. **Conclusion**: The results support the existence of a different factor structure in [R] Educational CPM between first- to second- grade elementary school students and new-old adults, on the one hand, and kindergarten students and old-old adults, on the other. This difference could possibly reflect the underdevelopment of inductive reasoning and executive functioning in the group of kindergarten students and the disorganization of them in the group of old-old adults.

Introduction

Researchers in the field of cognitive aging seem to agree that, on average, cognitive functioning declines with aging. Among the cognitive abilities that seem to be more affected by age is fluid intelligence, the capacity to solve problems in novel situations, independent of acquired knowledge [1, 2]. On the contrary, crystallized intelligence, i.e. the ability to use skills, knowledge, and experience, seems to remain intact [2].

Moreover, researchers have observed the general relationship between aging and development as findings in gerontological research have indicated that the collapse of intelligence in dementia patients causes retrogression to childhood and/or appears to reverse Piaget's developmental stages [3-5]. As stated by the retrogenic models, there is an inverse and progressive pattern of functional and cognitive decline observed in Alzheimer's Disease (AD) patients compared to the developmental acquisition of these capacities in children. Retrogenesis has been defined as the process by which degenerative mechanisms reverse the order of acquisition in normal development [6-8].

The findings regarding the retrogenic models suggest that comparisons should be made between the cognitive ability of these two groups of population, namely the developing children and the retrograding elderly people. This suggestion has been taken into account in the limited use, in assessing cognition in moderate and severe AD patients, of several screening instruments available for cognitive examination in infancy and childhood. For example, the application of the adapted and modified Ordinal Scales of Psychological Developmental (OSPD), developed by Uzgiris and Hunt for cognitive testing in infants, has been found to be superior to the use of traditional tests, such as the Mini-Mental State Examination (MMSE), in evaluating the cognitive capacity of patients with moderately severe and severe AD [9]. It was also reported that the use of test measures previously applied to infants and young children, based on Piagetian tradition, demonstrated residual cognitive capacity in subjects with severe AD previously considered untestable [6, 10]. Furthermore, childhood intelligence test measures, such as the Japanese version of the Binet scale, namely the Tanaka-Binet intelligence scale, has been found to be useful in evaluating cognition in moderate to severe AD patients [9].

Since there is a loss of cognitive abilities acquired during childhood before the appearance of clinically detectable dementia [5], comparisons of cognitive ability should also be made between the aforementioned groups of population, namely the developing children and the normal older adults or preclinical Alzheimer Disease (AD) patients.

As regards the preclinical AD patients with neurological changes it was reported that they do not demonstrate measurable cognitive decline on standard tests [11, 12]. More sensitive tests to detect early or preclinical stages of AD are desired, such as the Mini-Mental State Examination (MMSE), Wechler Adult Intelligence Scale-Revised (WAIS-R) and Wechler Memory Scale-Revised (WMS-R) which are evidence-based test batteries for memory decline and intelligence. However, these scales can be administered (have been developed and standardized) only to persons between 16 and 74 years of age [5].

In order for an approximate comparison between children's and older adults' cognitive ability to be correctly conducted, the administration of the same screening instruments to the two groups should be available [5, 13]. In addition, throughout the many attempts that have been made to develop test batteries for the early detection of dementia, it is also possible that the detection of preclinical AD could be more accurate through neuropsychological tests focused on the detection of developmental disturbances both in young children and older adults. Therefore, simple screening instruments, available for cognitive examination in infancy and childhood, are needed to allow the assessment of the cognitive ability in older adults, in a short period of time, which would assist in early detection of cognitive impairment.

Raven's Progressive Matrices

Raven's Progressive Matrices –Standard Progressive Matrices (SPM) and Coloured Progressive Matrices (CPM)– have commonly been employed in such investigations of group comparisons as they are considered to be among the best measures of general intelligence. Moreover, they have, both, been widely used in research, educational and clinical settings [14-18].

Raven's Progressive Matrices have been used for more than 70 years. In specific, J. C. Raven published the first version of his progressive matrices test in 1938 with a subtitle Perceptual Intelligence Test. The revised version, which was published in 1956, is known today as Standard Progressive Matrices (SPM). The test is non-verbal and was originally constructed as a test of eductive ability (from the Latin root "educere", meaning "to draw out'), which can be described as the ability to make "meaning out of confusion" or the ability to go "beyond the given to perceive that which is not immediately obvious" [19]. Most of us today would call it inductive reasoning or general reasoning.

Later, the original Standard Progressive Matrices (SPM) were supplemented by two more main versions -namely the easier Coloured Progressive Matrices (CPM) and the more difficult Advanced Progressive Matrices (APM)-, which followed the concept of standard matrices in all respects. Since then the three versions of the test (Standard, Coloured and Advanced Progressive Matrices) have been among the best-known and the most widely-used instruments for studying intelligence [20, 21]. Coloured Progressive Matrices (CPM) first appeared in 1947 as an alternative form of the Raven's Standard Progressive Matrices (SPM) and was revised in 1956. The CPM test was intended for children aged 5 to 11, special populations, and those who do not speak English. It comprises 36 items divided into three sets of 12 (Set A, A_B and B). In each item subjects are presented with an incomplete design and six alternatives among which one must be chosen that best completes the design. The items increase in difficulty, and so do the three sets, with set B containing the most challenging items. Knowledge acquired by answering previous items is necessary in order to answer a subsequent item, which implies that the respondent is expected to learn from items. The items of the CPM test are arranged to assess mental development up to the stage when a person is sufficiently able to reason by analogy and to adopt this way of thinking as a consistent method of inference [19].

The first standardization of CPM occurred in 1949 in the UK town of Dumfries. The sample consisted of 627 children between the ages of 5-11 years, representing 25% of the total school population. The test was sensitive to fluctuations in intellectual function, demonstrating good test-retest reliability (r = .80) [22]. In 1982, a follow-up normative study was conducted in Dumfries with a sample of 598 children. In 1998, the parallel version of CPM (CPM-P) was developed in conjunction with the SPM+ and included the creation of a parallel version of Set A_B. The newest edition of [R] CPM is the Raven's Educational CPM [19]. It has not incorporated any change in the items of the test but provided new normative data based on its U.K. standardization. The [R] Educational CPM standardization was conducted with a nation-wide stratified sample based on census data for geographical region, gender, race/ethnicity and parental educational level, a total of 608 children [19]. Apart from the UK normative studies, standardization of the CPM test has occurred in many countries around the world, such as the United States, France Argentina, Canada, Hong Kong, Germany, Romania, Slovenia, Lithuania, Turkey, Kuwait, South Africa, Pakistan, India (in nine Indian tribal groups) etc. Furthermore, a study aiming at providing normative data in older populations was conducted in the Netherlands with a representative age and gender stratified sample of 2.815 individuals aged from 55 to 85 years [23].

According to the [R] Educational CPM Manual [19], criterion-related validity report, there have been conducted a lot of studies that investigated the test's ability to predict performance in educational, cross-cultural and clinical settings. As regards the clinical settings, some studies have looked at the use of CPM with healthy adults and AD patients. It was reported that among normal subjects CPM loaded .66 on a factor described as the ability to achieve perceptual organization and among pre-operative dementia patients CPM loaded .88 on a factor including low verbal Wechsler scores, poor EEG patterns, emotional instability and lack of social interest [19]. Furthermore, a strong association was found between the drawing impairment of AD patients and their CPM score (r = -.59). Diagnostic differentiation between AD-type patients and those with vascular dementia, based on the use of their primitive responses to CPM, has also been reported. A correlation of .59 of the CPM scores with verbal WAIS scores and an internal consistency of the CPM test of .68, were also reported in studies with older adults [19]. Reliability measurements were also calculated from the [R] Educational CPM standardization sample. The constructors of Raven's Educational CPM [19] report a split – half reliability of .97 (N=608) They also found a parallel forms reliability of .87 between the CPM and the CPM-P, the former edition of the test, in an equating study on a sample of 83 children [19].

With regard to their factorial validity, although Raven's Progressive Matrices were initially developed as measures of the eduction of relations, they have been regarded by many researchers as appropriate measures of general intelligence (g-factor) according to the classic Spearman terminology [24-26]. However, this contention of a unidimensional nature of the ability measured by Raven's Progressive Matrices has been debated, with no signs of an end in sight.

Some researchers [27] found that APM measure two different processes, namely verbal-analytical and visual-spatial. Other researchers [28] found some sets in SPM to be unidimensional and some not. They applied a Rasch analysis on sets A to E of [R] PM and they found that Set A and the first half of Set B measured the perceptual process, while the second half of Set B and Sets C to E measured the analytic process. Furthermore, they concluded that other

processes were probably involved in the solution of half the items in Set E [28]. A lot of researchers [16, 29] identified in the factor structure of SPM three first-order factors that have been organized on the second-order g-factor. In specific, they confirmed the aforementioned [28] identification of a perceptual factor measured by Set A and the first items of Set B, and they also observed that the aforementioned [28] analytical factor could be separated in two distinct factors. These findings were also supported by researchers who argued that, although it is sometimes claimed that [R] Matrices provide an almost pure measure of g, there is evidence that the easier items in SPM and APM measure a perceptual or Gestalt factor distinct from the more analytic items in the rest of the tests [22].

Principal component analyses and nonlinear factor analyses both provided qualified support for both the multidimensional and the unidimensional models. Some researchers found that Rasch analyses more strongly suggest that APM are best described as being multidimensional [30], while other researchers concluded that, although the test yielded several specific first-order factors, it seems to be unifactorial as regards the second order [31]. As regards the factor structure of the CPM test in specific, from its inception, it has been acknowledged that the CPM test has a high g loading, with a visuo-spatial 'k'-factor involved to some degree [19]. Carlson noted a development in the reasoning process required for CPM solutions from perceptual to conceptual. This notification led him to relate CPM to Piagetian conservation concepts and found high loadings for both perceptual and conceptual items on the factor defined as simultaneous processing [32]. Further development of this work has led to the identification of three factors within the CPM items, namely, closure and abstract reasoning by analogy, pattern completion through identity and closure, and simple pattern completion [33, 34]. In a sample 180 first- to third- grade children, these factors were found to account for 36% of the total variance [34]. The aforementioned German findings were also confirmed in American studies [15, 35]. Principal component factor analyses were applied on data from 783 primary-grade children in California and the same three factors were found to account for 28% to 41% of the total variance [15].

However, other researchers analysed the findings of a sample of 166 gifted children on a little different way: They concluded that the CPM measures one factor, which has three related facets [36]. This position seems to support that probably the "most distinctive feature" of Raven's test "is its very low loading on any factor other than g" [26]. Furthermore, the authors of the Raven's Educational CPM manual [19] also claimed that the Item-Response-Theory-based item analysis demonstrates the scientific value of "general cognitive ability".

More recently, some researchers [31] suggest that it is crucial the possible constructive elements that form g (the cognitive processes, such as memory, learning, perception, metacognition etc., that the participants use during solving intelligence tests) to be taken into account in the discussion about the factor structure of intelligence tests, such as [R] PM. For them, the solutions with three or four factors identified in the items of CPM are also optimal. In their confirmatory factor analyses of the test, in the models with the explicitly introduced higher-order general factor the correlations of the primary factors with the general factor were between .50 to .90. However, both the models with and without the higher order factor were found to fit data equally well. As regards the findings provided from the application of factor analysis by age, they found that factor solutions are practically stabilized after the age of five when a factor pattern that is later repeated at all ages is already form. This factor pattern reflects the difficulty of the CPM's items. On the contrary, at the age of four, the factors do not resemble the factors obtained at older ages [31].

Aim of the study

Based, firstly, on findings in the field of cognitive aging, supporting that fluid intelligence (inductive reasoning) increases rapidly in the early years of life and declines with aging [1, 2], and, secondly, on the hypothesis of "retrogenesis", the aim of the present study was the comparison of the, highly correlated with fluid intelligence [37], general cognitive ability (g) between the developing children and the healthy older adults. The comparison has been conducted through the investigation of the latent structure qualitative changes in [R] Educational CPM from age to age, using Confirmatory Factor Analyses (CFA). Comparing pair-wise the four groups of our sample (first- to second- grade elementary school students with new-old adults) and (kindergarten students with old- old adults), the latent structure in [R] Educational CPM is expected to differentiate between first- to second- grade elementary school students and new-old adults, on the one hand and kindergarten students and old-old adults, on the other (Hypothesis 1). In specific, we expected to find similar latent structure in [R] Educational CPM for first- to second- grade elementary school students and new-old adults (Hypothesis 2a), and similar latent structure in [R] Educational CPM for kindergarten students and old-old adults (Hypothesis 2b).

Method

Participants and Procedure

The total sample consisted of four groups of individuals: a group of kindergarten students, a group of first- to second-grade elementary school students, a group of new-old adults, and a group of old-old adults.

The first group comprised 42 kindergarten students 5 to 6 years old (mean age = 68.1 months, age range: 61-75 months). Of the 42 participants, 16 were boys (38.1%) and 26 were girls (61.9%). The second group included 56 first- to second- grade elementary school students 6 to 8 years old (mean age = 85.45 months, age range: 74-98 months). Of the 56 participants, 22 were boys (39.3%) and 34 were girls (60.7%). All the children attending regular classrooms, without a history of learning difficulties (based on the school records and student reports) in two preschool institutions (one public and one private) and three primary schools (two public and one private) of medium and high socioeconomic status, in the city of Ioannina in Epirus (a province in the West of Greece). All the young participants, additionally to the [R] Educational CPM, completed the Greek version of the Mini Mental State Examination [MMSE; 38, 39] in order for a brief estimate of their overall cognitive functioning to be provided [for the kindergarten students: M = 22.67 (*SD* = 3.66), and for first- to second- grade elementary school students: M = 26.95 (*SD* = 2.28)]. These means are consistent with previous findings

[5, 13]. In collaboration with the school committees, parents gave their written statement of consent prior to the participation of their children in this study and then they completed an individual-demographics form. Children's testing in [R] Educational CPM and MMSE was performed in their school environment, by trained interviewers under the surveillance of a psychologist. No time limit was assigned for the completion of the tests and all young participants were informed that they were free to withdraw from testing at any time.

Given that the [R] Educational CPM test was also intended for use with older adults, two groups of older adults were tested. In specific, one group comprised 118 new-old adults (mean age = 71.33 years, age range: 61-79 years). Of the 118 participants, 45 were men (38.1%) and 73 were women (61.9%). The second group of older adults included 27 old-old adults (mean age = 83.04 years, age range: 80-88 years). Of the 27 participants, 10 were men (37.0%) and 17 were women (63.0%). Exclusion criteria for both groups were history of neurological conditions or psychiatric diseases, alcohol or drug abuse, severe head trauma, profound visual impairments, and verbal incomprehension. Moreover, all the participants additionally completed the Greek version of the Mini Mental State Examination [MMSE; 38-39]. In specific, the subsample of older adults consisted of 122 normal participants (103 new adults & 19 older adults), who had MMSE scores between 25 and 30 points, and 23 participants (15 new adults & 8 older adults), who had MMSE scores between 20 and 24 points falling in the Mild Cognitive Impairment (MCI) to mild dementia range [38-39], -although they had not been diagnosed by consultant neurologists and psychiatrists as meeting diagnostic criteria for possible dementia. All the participants were community dwelling adults - volunteers recruited by the researchers through seniors' centers. They were residents of Thessaloniki and Kozani (a town in the province of West Macedonia in Greece). Participants were examined at an individual basis, either at the center recruited, or in their own home. No time limit was assigned for the completion of the examination and the participants were informed that they were free to withdraw from testing at any time. For all the participants informed consent was obtained and then they completed an individual - demographics form. It should be noted that the subsample of older adults included an overrepresentation (57.2%) of persons with 9 years of formal education or fewer.

Instrument

Raven's Educational Coloured Progressive Matrices (R-CPM).

Raven's Educational Coloured Progressive Matrices are designed to assess the intellectual processes of young children ranging in age from 4 to 11 years [19]. The book form of the [R] Educational CPM contains three sets (A, A_B, and B) of 12 items of coloured large-print drawings each. In each item subjects are presented with an incomplete design and six alternatives among which one must be chosen that best completes the design. Every correctly solved item results in 1 point. Sum scores may be used for every set (score range 0-12) or for the total [R] CPM test (score range 0-36).

Statistical analysis

As has already been mentioned the aim of the present study was the investigation of the latent structure qualitative changes in [R] Educational CPM from age to age, using Confirmatory Factor Analyses (CFA). According to the aforementioned findings in the introduction section, it is obvious that previous empirical works have implied several a priori competing models for CPM dimensionality. It should be also noted here that the present study did not aim to test extensively the constructive validity and the rest psychometric properties of [R] Educational CPM in Greek population, since the Greek standardization of [R] Educational CPM is in progress [40]. Furthermore, the sample size of the present study was inadequate for the conduction of CFA models testing the dimensionality of the [R] Educational CPM (including the 36 items of the test) in every one of the four groups of the sample. It is recommended that the sample size requirements, for SEM techniques, would be at least five observations per estimated parameter [41]. Hence, in order for the sample size to be adequate, at least 180 persons should participate in every group.

Because of the relatively small sample size of each group, analyses were not run at the item level. Instead, the covariance matrix was based on three total scores (measured variables), namely, total raw score for Set A, total raw score for Set A_B and total raw score for Set B. Hence, the sample size for the conduction of CFA had to exceed 15. Thus, the sample size of each one of the four groups exceeded the minimum recommended level for performing confirmatory factor analysis.

Considering CFA -a structural equation modeling (SEM) technique for analyzing structural models with observed variables, is adequate for examining the latent factor structure of the [R] Educational CPM test for every group of our sample, using sum scores of each one of the three observed variables (sets of the test). Hence, we used CFA in order to test the hypothesis that individual variability across CPM measured variables (total raw scores of each of the three sets) can be modeled by one latent variable (a single underlying factor). Confirmatory factor analysis was conducted in EQS Version 6.1 [42] and performed on the five covariance matrices, which stemmed from the total sample and each one of the four groups of participants, using the Maximum Likelihood (ML or ML ROBUST) estimation method. The Wald test was used to test the need for the estimated parameters and to suggest a more restricted model.

The indices of each one of the five models, which were provided from the application of CFA in each of the five covariance matrices, were the following: $\chi^2 = 0.00$, $df = 0$, p = undefined, NFI = 1.00, while NNFI, CFI and RMSEA were not computed because the degrees of freedom were zero. These models have been solved and should be considered as just-identified [43]: "In fact because the numbers of knowns equals the number of unknowns, in just-identified models, there exists a single set of parameter estimates that perfectly reproduce the input matrix." The input matrices of the aforementioned models consist of 6 knowns (3 variances, 3 covariances), and the models consist of 6 freely estimated parameters: 3 factor loadings and 3 indicator errors, with the variance of the latent variable to be fixed to 1.0. Thus, although just-identified CFA models can be fit to the sample input matrix, goodness-of-model-fit evaluation does not apply because, by nature, solutions such the aforementioned, always have perfect fit [43].

Results

Testing Latent structure of [R] Educational CPM in the total sample
Initially, we tested the one-factor CFA model [the one-factor model in which all three measured variables loaded on a single latent variable] in the total sample (Model A). Confirmatory factor analysis fully verified the one-factor structure -based on 3 measured variables/summated items- of [R] Educational CPM for the total sample [$\chi^2(0, N = 243) = 0.00$, p = undefined, NFI = 1.00]. NNFI, CFI and RMSEA were not computed because the degrees of freedom were zero. According to the suggestions of the Wald test all the parameters' loadings of the Model A were statistically significant. Thus, we derived one factor (latent variable), that probably explains the variance of participants' performance on [R] Educational CPM. For the total sample, Cronbach's α coefficient was .86.

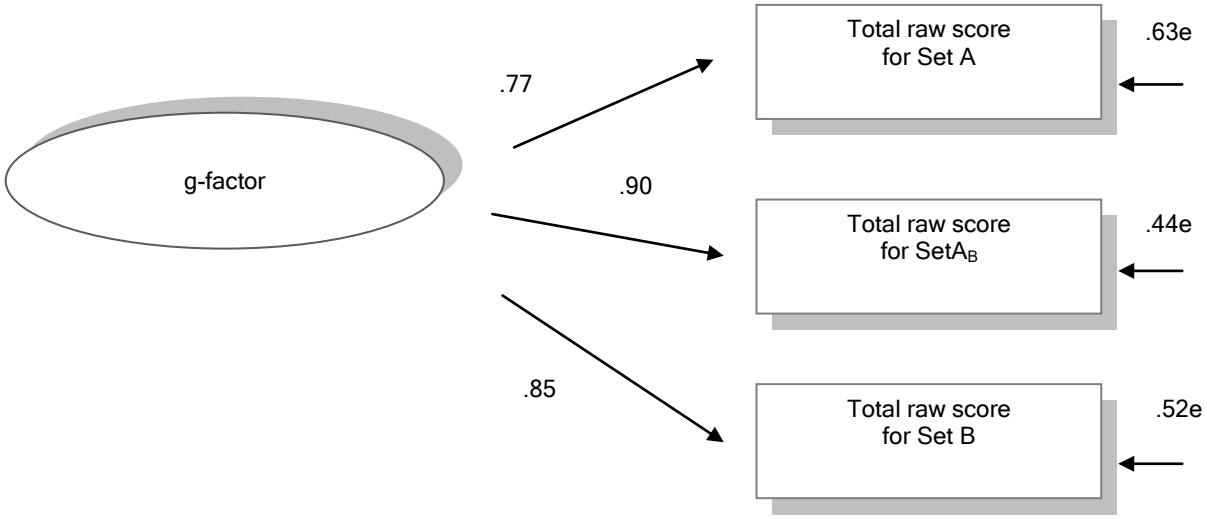

Figure 1. The underlying structure of the single g latent factor in the total sample (standardized solution).
*All loadings drawn indicate significant associations (p < 0.05). **e = measurement error

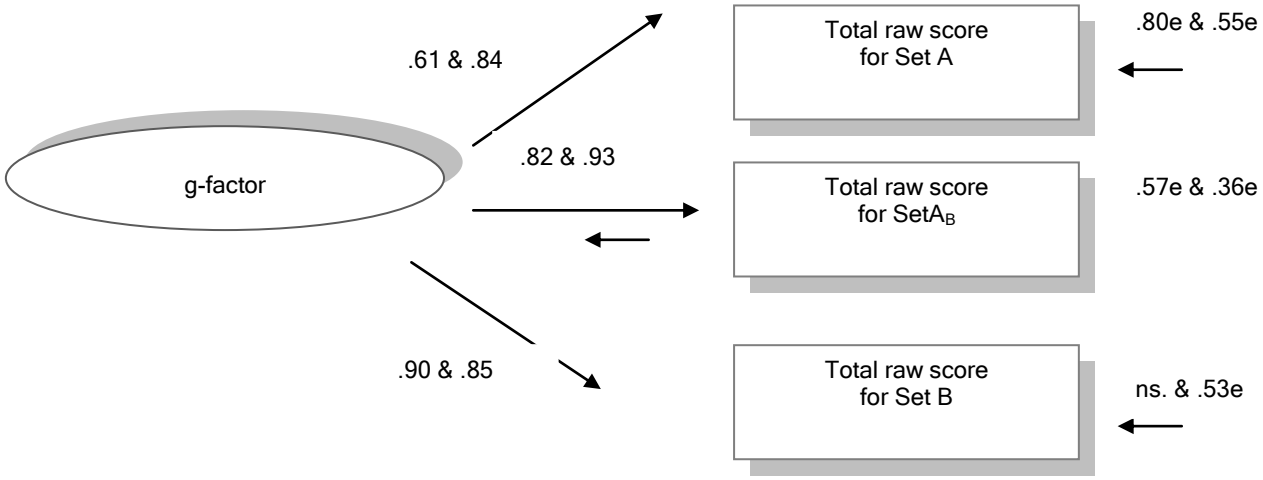

Figure 2. The underlying structure of the single g latent factor in the subsamples of elementary school students and new-old adults (standardized solution). *All loadings drawn indicate significant associations (p < 0.05). **e = measurement error

Testing Latent structure of [R] Educational CPM in the subsamples of elementary school students and new-old adults
In order to compare the latent structure in [R] Educational CPM between elementary school students and new-old adults, we tested the one-factor CFA model [the one-factor model in which all three measured variables loaded on a single latent variable] in the group of first- to second- grade elementary school students (Model B). Confirmatory factor analysis verified the one-factor structure -based on 3 observed variables/summated items- of the [R] Educational CPM for the group of first- to second- grade elementary school students [$\chi^2(0, N = 56) = 0.00$, p = undefined, NFI = 1.00]. NNFI, CFI and RMSEA were not computed because the degrees of freedom were zero. According to the suggestions of the Wald test, all the parameters of the Model B were statistically significant, except for the residual of one of the measured variables, namely the residual of the total raw score for Set B (p = .19). Thus, we derived one factor (latent variable), that probably explains the variance of the elementary school students' performance on [R] Educational CPM. For the group of first- to second- grade elementary school students, Cronbach's α coefficient was .80. Then, we tested the one-factor CFA

model [the one-factor model in which all three measured variables loaded on a single latent variable] in the group of new old adults (Model C). Confirmatory factor analysis fully verified the one-factor structure -based on 3 latent variables/summated items- of the [R] Educational CPM for the group of new-old adults [$\chi^2(0, N = 118) = 0.00$, p = undefined, NFI = 1.00]. NNFI, CFI and RMSEA were not computed because the degrees of freedom were zero. According to the suggestions of the Wald test all the parameters' loadings of the Model C were statistically significant. Thus, we derived one factor (latent variable), that probably explains the variance of the new old adults' performance on [R] Educational CPM. For the group of new-old adults, Cronbach's α coefficient was .89.

The comparison of the CFA Model B with the Model C indicates a similar latent structure in [R] Educational CPM for first- to second- grade elementary school students and new-old adults and verified Hypothesis 2a.

Testing Latent structure of [R] Educational CPM in the subsamples of kindergarten students and old-old adults

In order to compare the latent structure in [R] Educational CPM between kindergarten students and old-old adults, at first we tested the one-factor CFA model [the one-factor model in which all three observed variables loaded on a single latent variable] in the group of kindergarten students (Model D1). Due to the statistically significant excess kurtosis of this group of the sample, Model D1 was computed using the Maximum Likelihood (ML ROBUST) estimation method. However, during our trial to test Model D1, the EQS program [42] warned that corrected chi-square could not be calculated due to numerical difficulties. Since the Satorra-Bentler chi-square was impossible to be computed as well as the rest goodness-of-model-fit indices, because of the nature of the model [43] (see also Model A, B, & C), the provided solution was not acceptable. Hence, despite the distributional misspecification (significant excess kurtosis), the confirmatory factor analysis was re-performed on covariance matrix using the Maximum Likelihood (ML) estimation procedure (Model D2) [42]. According to its indices [$\chi^2(0, N = 42) = 0.00$, p = undefined, NFI = 1.00], it seemed that Model D2 should be also considered as just-identified (see Models A, B, & C) [43], and fits the data better than Model D1 of this set of analysis. However, according to the suggestions of the Wald test, the one-factor structure -based on 3 latent variables/summated items- of the [R] Educational CPM was not confirmed for the group of kindergarten students because, although the rest of the parameters' loadings of Model D2 were statistically significant, the variance of the single latent variable (factor) was not found to be statistically significant (p = .07). Thus, we did not derive one factor, that could explain the variance of the kindergarten students' performance on [R] Educational CPM. For the group of kindergarten students, Cronbach's α coefficient was .71.

Finally, we tested the one-factor CFA model [the one-factor model in which all three measured variables loaded on a single latent variable] in the group of old-old adults (Model E). According to its indices [$\chi^2(0, N = 27) = 0.00$, p = undefined, NFI = 1.00], it seemed that Model E should be also considered as just-identified (see Models A, B, C, & D2) [43] and fits the data perfectly. However, according to the suggestions of the Wald test, the one-factor structure -based on 3 latent variables/summated items- of the [R] Educational CPM was not confirmed for the group of old-old adults because, although the rest of the parameters' loadings of Model E were statistically significant, the variance of the single latent variable (factor) was not found to be statistically significant (p = .07). Thus, we did not derive one latent factor, that could explain the variance of the old-old adults' performance on [R] Educational CPM. For the group of old-old adults Cronbach's α coefficient was .72.

The comparison of the CFA Model D2 with Model E indicates a similar pattern of structure in [R] Educational CPM for kindergarten students and old-old adults and verified Hypothesis 2b.

To summarize, the aforementioned findings confirm Hypothesis 1 and support the existence of a different factor structure in [R] Educational CPM between first- to second- grade elementary school students and new-old adults, on the one hand, and kindergarten students and old-old adults, on the other.

Discussion

Although we stuck to the standard methodology of confirmatory research, the present study should not be understood as testing the hypothesis of unidimensionality in [R] Educational CPM. The aim of the present study was the comparison of the general cognitive ability between the developing children and the retrograding older adults through the investigation of the latent structure qualitative changes in [R] Educational CPM from age to age, using Confirmatory Factor Analyses (FCA) and testing a conventional unidimensional model.

With regard to dimensionality, for the groups of elementary school students and new-old adults, the results of CFA seem to support the existence of a single latent g-factor measured by [R] Educational CPM. For the groups of kindergarten students and old-old adults the existence of a single latent g-factor measured by [R] Educational CPM was not confirmed, since its variance was not found to be statistically significant.

The aforementioned findings are consistent with previous findings [31] indicating that the factor solutions are stabilized after the age of 5-6. Until then, the factor structure of [R] CPM does not resemble much the factor structure obtained in older ages. Since inductive reasoning or general reasoning (the current name of eductive ability) is one of the main possible constructive elements that form g, a possible explanation for these findings could be that inductive generalization is not a unitary cognitive operation, but it is possible to start with perception and only in the end to develop pure induction [44, 45]. Some researchers [31] provided another explanation, taking also into account a possible component of g, namely the executive functioning. According to them, the delay of stabilization of the CPM factor structure at earlier ages (before the age of 5-6) could reflect lack of metacognitive and self-regulative processes -two of the main components of executive functioning- and could be attributed to the inflexible solving strategy, the poor management of goal activity and the weak mechanisms of control [31, 46-51].

The similar, not unidimensional structure of the [R] Educational CPM test that was observed, in the present study, between the group of kindergarten students and the group of old-old adults, is possible to indicate a qualitative change, perhaps a start of disorganization, either in the inductive reasoning, and/or in the executive functioning of the old-

old adults comparing to that of the new-old adults [46-51]. This finding is consistent with the general admission in the field of cognitive aging, stating that cognitive functioning declines with aging and fluid intelligence –which is highly related to inductive reasoning– is among the cognitive abilities that seem to be more affected by age [1, 2].

In general terms, the different pattern in the latent factor structure of the [R] Educational CPM test, that was found in the present study, between the groups of kindergarten students and old-old adults, on the one hand, and the groups of first- to second- grade elementary school students and new-old adults, on the other, is a supporting finding with regard to the hypothesis of "retrogenesis". It should be also noted that the disorganization of general cognitive ability as regards two of its components, namely inductive reasoning and executive functioning [46-51], was found to be present before the appearance of clinically detectable dementia in the majority of the participants in the subsample of old-old adults. This finding seems to be in line with recent findings indicating that a large proportion of healthy old-old adults show memory decline which may represent the early stages of a potentially more severe cognitive impairment [5, 11-12]. Furthermore, the concept that normal old-old adults, as well as MCI patients, retrograde to the levels of early childhood, regarding their general cognitive ability, simplifies the understanding of them and contributes to their appropriate care from their family and caregivers.

In conclusion, this is a pilot study of [R] Educational CPM conducted in a Greek population of young children and older adults. More research is also needed to further validate and refine, in other cultural contexts, the different pattern in the structure of g, -as it is measured by [R] Educational CPM-, that was found in the present study, between the groups of kindergarten students and old-old adults, on the one hand, and the groups of first- to second- grade elementary school students and new-old adults, on the other. The results of our findings, with the size of the sample used, support the usefulness of [R] Educational CPM as a sensitive neuropsychological test for the detection, in the old-old adults, of the differentiation and/or the decline of the general cognitive ability acquired during childhood. In order for the applicability of [R] Educational CPM to be assessed in Greek older adults, normative data have to be provided for this population. This would permit us to test further the quality of the [R] Educational CPM test as an appropriate neuropsychological instrument for screening general cognitive ability in normal older adults and/or preclinical dementia patients as well.

The authors declare that they have no conflicts of interest.

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Emotion decoding from dynamic visual cues in older adult stroke patients: a preliminary study

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Abstract

Aim: Social perception is very important for social interaction. Difficulties in emotional recognition might lead to communication failures. Damages affecting neural networks involved in emotion recognition may cause deficits in social cognition and social life. The aim of the present study was to examine the ability of emotion recognition in older adult stroke patients. **Method:** Basic emotion recognition performance of fifteen older adult stroke patients and fifteen healthy controls were compared. The one third of the participants in both groups was men and the two groups did not differ si age and educational level. In the patient group the 53.3% had a light stroke and in average 6.2 years were passed since the stroke. The procedure took place at participants' homes within the social program "Help at Home". The Emotion Evaluation Test – Part 1 from the "The Awareness of Social Inference Test" developed by McDonald and colleagues (2003), which evaluates the recognition of basic emotions from dynamic cues, was the main assessment tool. **Results:** The results showed statistically significant lower-level recognition of happiness and a strong tendency of a higher-level recognition of negative emotions in the patient group, compared to healthy older adult group. **Conclusion:** The results are consistent with leading socioemotional theories of lifespan development, according to which, the "positivity effect" that characterizes older adult's socioemotional behaviour, is reversed to a "negativity bias", when cognitive control processes are not at an adequate level that could support older adult's motivational preference to cognitively process positively-valenced information.

Introduction

The two basic skills required in order to maintain normal social interaction are the expression of our own emotions and the recognition of the emotions of the other. As people grow older, they experience memory loss and cognitive slow-down that, to a greater or lesser extent, influence the quality of relations in their daily routines [1, 2]. The recognition of emotions requires a series of cognitive processes: discrimination of perceptual details, recognition of characteristic (e.g., visual) patterns, and comparison with prototypes stored in the long-term memory system, to name a few. All these processes are regulated by higher-order cognitive functions, namely the executive functions. Executive functions represent the cognitive – behavioural "expressions" of the activation of the frontal lobe, which monitors and interacts with other brain structures involved in emotion recognition [1, 2].

Emotionally competent individuals are characterized by optimal functioning of emotion production and emotion perception. Emotion production competence refers to the appropriateness of the total pattern of bodily and behavioral changes as an adaptive response to a relevant event, allowing the organism to successfully cope with its consequences, Emotion perception competence refers to the ability to accurately perceive and interpret the emotional state of the other in social intercourse, based upon facial, vocal, and bodily expression [3].

Emotion recognition is an important skill related to social cognition. The emotional interpretation of stimuli such as facial expression, eye contact, body posture and movement, tone of voice, and broader contextual cues allows people to comprehend and predict other's behaviour, provide support, avoid conflict, and regulate their emotions [4]. Emotion recognition could be related to changes in personality dimensions during aging, or it could be a separate ability. Previous studies have demonstrated reliable correlations between the ability to recognize emotions and personality dimensions. In particular, individuals who score highly on measures of the 'openness to experience' trait are more successful in recognizing emotional expressions [1].

Difficulties in emotion recognition are therefore considered a crucial factor in inadequate communication, and are associated with interpersonal problems that might lead to development and maintenance of psychopathology. Numerous studies have found that older adults are less adept at identifying emotions being expressed mainly via visual cues compared to younger adults [5-7]. Specific types of social functioning impairment, including reduced social competence and interest, poor interpersonal functioning and communication, which are associated with difficulties in emotion recognition, lead to reduced quality of life and inappropriate social behaviour [8]. Specifically, the message gleaned from reviews of existing research on age differences in recognizing basic emotions (i.e., happiness, surprise, sadness, anger, fear or anxiety, and disgust) is that age-related decline is generally greater for specific negative emotions – especially anger and sadness – than for specific positive ones [8-10].

Phillips, MacLean, and Allen (2002) [11] found that there were no age effects on the ability to decode emotions from verbal material .On the contrary, older people were less able to identify facial expressions of anger and sadness, and showed poorer ability to identify Theory of Mind from pictures of eyes. Compared with healthy controls, participants with unilateral or bilateral amygdala damage were impaired when recognizing social emotions; moreover, they were more impaired in recognition of social emotions than in recognition of basic emotions, and they were impaired also when asked to recognize social emotions from the eye region of the face, alone [12]. At this point it must be mentioned that as 'basic emotions' are considered certain emotions that appear to be universally recognized, according to the existing literature. In fact, the following six emotions are classified as basic: anger, disgust, fear, happiness, sadness, and surprise [12]. On the other hand, social emotions are emotions requiring at a great extent the representation of the mental states of other people, that is, Theory of Mind. Examples are embarrassment, guilt, shame, jealousy, envy, and pride. Hence, it is obvious by definition that social emotions are tightly linked with social cognition, while basic emotions represent a more primitive, instinctive part of it [1, 12].

At the neural level, there are a wide range of neural systems involved in recognizing and labelling facial expressions of emotion, with frontal and temporal systems mainly involved. Some temporal areas such as the amygdala and fusiform cortex have been argued to have a general role in responding to all facial expressions. Other important regions are the dorsolateral prefrontal cortex, ventral striatum, superior temporal sulcus, as well as visual processing areas in the parietal and occipital lobes. The basal ganglia and insula are specifically involved in decoding facial expressions of disgust, whereas the amygdala is particularly implicated in decoding facial expressions of fear. In general, auditory emotions activate numerous brain regions, but again place a substantial load on frontal networks [8].

Another neural pattern in emotion recognition has been shown by Kucharska-Pietura and colleagues (2003), who concluded that patients with brain damage in right hemisphere were markedly impaired relative to left hemisphere damaged and healthy controls on the following tests' performance: labelling and recognition of facial expressions, and recognition of emotions conveyed by prosody [13]. In another research [14], subjects with bilateral amygdala damage did not show the same performance as regards certain expressions of negative emotions: they were more accurate in recognizing scenes showing anger with faces erased than with faces present, an effect resulting in part from highly abnormal recognition of certain angry facial expressions. Bilateral amygdala damage thus disproportionately impairs recognition of certain emotions from complex visual stimuli when subjects utilize information from facial expressions. Furthermore, in a recent study, it was found that traumatic brain injury (TBI) participants' recognition of basic emotions, as well as their capacity for mental state attribution, were significantly reduced relative to healthy controls. Performance on both of these measures was strongly correlated in the healthy control, but not in the TBI sample. In contrast, in the TBI (but not the control) sample, Theory of Mind was significantly correlated with performance on phonemic fluency, a measure of executive functioning considered to impose particular demands upon cognitive flexibility and self-regulation. These results are consistent with other evidence indicating that deficits in some aspects of executive functioning may at least partially underlie deficits in social cognition following TBI, and thus help explain the prevalence of social dysfunction in TBI [15].

More broadly, the majority of studies that have examined age effects on emotions have taken the sociocognitive perspective. Socioemotional Selectivity Theory is a life-span theory of motivation that predicts enhanced emotion regulation with age. According to the theory, time perspective is the dominating force that structures human motivations and goals. The theory contends that humans have a conscious and subconscious awareness of their time left in life, and that perceived boundaries on time direct attention to emotionally meaningful aspects of life. In contrast, when time is perceived as limited, emotional experience assumes primacy and people are motivated to monitor and select their environments to optimize emotional meaningfulness and emotional functioning. According to the theory and the respective empirical evidence, younger people who are approaching the end of life show similar motivational changes. Consistent with the theory, older age is associated with improved emotion regulation. According to the socioemotional selectivity theory, the perceived limited time left in one's life generates what is known as the positivity effect, a developmental pattern in which a disproportionate preference for positive information emerges during aging [16]. When circumstances do not allow for goal-directed processing (i.e., splitting attention between multiple tasks), the "positivity effect" appears to be reversed to an "automatic negativity bias" in older adults' cognition. This is not surprising given that the control of affect needs increased neural activation in executive function regions including the prefrontal cortex. Considering that these regions deteriorate significantly with advancing age, older adults need to compensate for these deficits by recruiting more cognitive resources in their efforts to regulate affect, compared to young adults. Therefore, older adults are successful in affect regulation including the mechanism of the "positivity effect", only when they can devote considerable amount of cognitive control to regulation [4, 17-19].

In support of the Socioemotional Selectivity Theory, the major conclusion of a recent empirical work [20] was that cognitively healthy older adults, due to motivational shifts related to future time perspective that is perceived as limited, display a preference in processing positively valenced information, which is known as the "positivity effect" bias, with regard to basic emotions' decoding from dynamic visual cues. This bias is mainly reflected in their excellent ability to recognize happiness together with their lower ability to recognize basic negatively valenced emotions, compared to demented older adults. Inversely, demented persons, probably due to their diminished cognitive control resources, appear to reverse the "positivity effect" to an over-determined

"negativity bias" in basic emotions' decoding from dynamic visual cues. This is primarily reflected in their significantly lower ability to recognize happiness and their higher ability to decode three negatively valenced emotions, namely anger, sadness, and anxiety, compared to cognitively healthy older adults.

Based on the aforementioned theory and research, the aim of the present study was to fill the literature gap by identifying the pattern of differences between stroke patients and "healthy" older adults in basic emotion decoding from dynamic visual cues, on the basis of both motivational and structural factors. Given that older adults after a stroke probably have deficits in cognitive control, we expected that they would not perform as well as healthy older adults on basic emotion recognition, in general (Hypothesis 1). Due to the same reason, a second hypothesis formulated was that stroke patients would have difficulties in recognizing positively-valenced emotions and especially, happiness, in sharp contrast to the "healthy" older adult participants who were expected to display an excellent performance on happiness recognition (Hypothesis 2).

Method

Participants and Procedure

The sample comprised a total of 30 older adults from Greece who participated voluntarily in the study. All participants gave informed consent, and their anonymity was preserved. They were examined on an individual basis at a place of their own choosing. For all control and stroke participants informed consent was obtained and then they completed an individual – demographics form. All the participants additionally completed the Greek version of the Mini Mental State Examination [MMSE; 21, 22]. The MMSE was used to provide an estimate of overall cognitive functioning. They also completed the Greek version of the Geriatric Depression Scale – 15 [GDS-15; 23, 24] to assess current depression symptoms. This was followed by the main assessment of the study, which was the assessment of emotion recognition as measured by the Emotion Evaluation Task (EET) of the TASIT [4, 25, 26, 27]. Exclusionary criteria for the "healthy" older adult participants were a Mini-Mental State Examination [21,22] score of less than 24 and a Geriatric Depression Scale-15 score of more than 7 [23, 24]. Other exclusionary criteria for all participants were: drug or alcohol abuse, secondary neurological disorders (e.g., epilepsy, dementia), and other psychiatric diagnoses. Participants who had difficulties with vision or hearing were also excluded. As shown in Table 1, the 30 participants were divided into two groups: older adult stroke patients (Group A) and healthy older adults (Group B). Brain-damaged participants were included if they have experienced a single episode of cerebrovascular accident (ischemic stroke or haemorrhagic infarct) localised in one hemisphere (In average 6.2 years were passed since the stroke). Most neurological patients had motor deficits on the contralateral side to their lesions at the time of illness onset (see Table 1).

The two groups did not differ significantly in age, $t(13) = .14$, $p > .05$. Three educational levels were defined according to the number of years of education: low, middle, and high educational level. It should be noted that all participants tended to have a low educational level. They did not differ significantly in educational level (EL), $t(2) = .56$, $p > .05$. Also, the two groups did not differ significantly in gender, $t(1) = 1.00$, $p > .05$. However, relative to healthy controls, the stroke group had a significantly lower score in the MMSE, $F(1, 28) = 4.659$, $p = .04$, $n2 = .143$. The two groups did not differ in their GDS-15 scores, $F(1, 28) = .058$, $p = .77$, $n2 = .003$.

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Table 1. Participants' distribution according to age, gender, and educational level

	Gender		Age			Education			GDS			MMSE		
Group	Male	Female	Range	Mean	SD	Low (0-9 years)	Middle (10-12 years)	High (>13 years)	Range	Mean	SD	Range	Mean	SD
Group A (n=15)	33,30%	66,70%	65-71	68	2	60%	33,30%	6,70%	1-6	3,80	1,52	26-30	27,20	1,14
Group B (n=15)	33,30%	66,70%	65-81	72,2	7,6	53,30%	26,70%	20%	0-6	4,00	2,17	24-30	28,53	2,10

*GDS-15, Geriatric Depression Scale -15; MMSE, Mini-Mental State Examination; Group A = stroke patients; Group B = "healthy" older adults

Tools

TASIT was designed to provide an ecologically valid assessment of core areas of social perception. It was designed to assess the ability to interpret emotional expression, as well as other verbal and non-verbal signals, in order to make judgments about the mental and emotional state of the speakers and the meaning of their conversations. The test comprises a series of videotaped vignettes employing professional actors. It has three parts, each with alternate forms: (1) Emotion Evaluation Test, (2) Test of Social Inference (Minimal), and (3) Test of Social Inference (Enriched). Emotion Evaluation Test (EET) of TASIT (with alternate forms A and B) comprises 28 video vignettes of professional actors portraying one of the six basic emotions that are widely accepted as universals: happiness, sadness, anger, fear - anxiety, revulsion (disgust), and (pleasant) surprise. It also includes vignettes of actors portraying emotionally neutral expressions. All scripts are ambiguous monologues or dialogues devoid of specific emotional content [28]. Evidence for construct validity is derived from its relationship to

conventional neuropsychological tests, experimental tests of social perception, and real-world performance. In addition, research using TASIT to examine deficits in social perception in traumatic brain injury, schizophrenia, frontotemporal dementia, Alzheimer's disease, and stroke attest to its sensitivity as a clinical assessment tool [25].

In more detail, the EET - FORM A is the first part of the Awareness of Social Inference Test. Specifically it comprises 28 short (15–60 s) videotaped vignettes of people interacting in everyday situations. In fact, the people are Method actors who have been trained to elicit real emotions in themselves. The EET also uses visual and auditory contextual cues to assess emotion decoding systematically. In some scenes there is only one actor talking. Other scenes depict two actors. In these cases, instructions are given to focus on one actor. The 'target' actor in each scene enacts the script according to one of the six basic emotions or no particular emotion (i.e. neutral). After viewing each scene, the participant is asked to choose the emotion displayed by the actor from a list of six emotional categories and one non-emotional category (neutral) displayed on a response card. There are five response cards, and each card presents the seven categories in a different order. The 28 scenes comprise four portrayals of each emotion, as well as neutral condition, in quasirandomized order. All the scripts are neutral in content and do not lend themselves to any specific emotion. However, as the test was developed in English, we decided to administer it with the sound turned off, so as to focus on the participant's ability to recognise dynamic visual cues. Administration of the EET typically takes 15-25 min, depending on the participant's age and condition. The EET was administered according to the standard procedure outlined in the relevant manual. To familiarize the participant with the task requirements a practice item preceded the main task [4]. The reliability of the EET's psychometric qualities for test-retest, based on the performance of adults with severe traumatic brain injury, was estimated to be moderate (r = .74). In relation to the EET's construct validity, it was found to be significantly correlated with the following: premorbid IQ; information processing speed; new learning of social information and, specifically, faces; executive function as measured by a socially relevant task and by a geometric problem-solving task measuring visuospatial and analogical reasoning; and the Ekman photo-labelling and matching tasks as measures of social perception [26-27].

As regards the structural validity of the EET, when it is administered as a test of decoding only visual cues, Moraitou and colleagues (2013), using Structural Equation Modelling (SEM) technics, confirmed a model for the factorial structure of the EET in adults. In this model five EET items related to specific emotion decoding ('surprised', 'sad', 'angry', 'anxious', and 'disgusted') were set to load on one factor labelled 'Decoding of Uncertain Emotional Displays'. Moreover, the observed variable 'happiness recognition' and the latent factor 'Decoding of Uncertain Emotional Displays' were allowed to co-vary with the observed variable 'neutral expression recognition' but not with each other: The chi-square goodness of fit test was not statistically significant, resulting in the acceptance of the null hypothesis of good fit, Satorra-Bentler scaled $\chi 2$ (14, n = 208) = 18.36, p = .191. The Comparative Fit Index (CFI) had a value of .99, indicating strongly reasonable fit, and the Root Mean Square Error of Approximation (RMSEA) index was .04 (90%CI: .00 – .08), indicating close approximate fit for this model [3]. Hence, according to the confirmed factorial structure of the EET, it seems that decoding of all basic emotions - except happiness- from dynamic visual cues follows the same neuropsychological mechanisms, and a basic step in emotion decoding involves recognizing whether information presented is emotional or not. In the same study, age was found to negatively affect the ability to decode basic negatively-valenced emotions as well as pleasant surprise. Happiness decoding from visual cues was the only ability that was found well-preserved with advancing age [4].

Results

The data gathered by the EET administration were firstly analyzed with a 2 x 7 mixed ANOVA with the between-subjects variable of group type (A: stroke patients - B – "healthy" older adults) and the within-subjects variable of emotion type (happy, surprised, angry, anxious, sad, revolted, neutral). The analysis indicated that there was a main effect of emotion type, F (6, 23) = 11.57, p < .001, $\eta 2$ = .75. There also was a marginal interaction effect, F (6, 23) = 2.26, p = .05, $\eta 2$ = .39.

To analyze the interaction between group and emotion type observed for EET, tests of simple effects were conducted. For almost all of the emotions and the neutral condition, group was not a significant simple main effect: for pleasant surprise, F (1, 28) =1.522, p = .23, n2 =.05, for neutral expression, F (1, 28) =.149, p =.70, n2=.05, for sadness, F (1, 28) =1.200, p =.13, n2 =.08, for anger, F (1, 28) =1.318, p = .26, n2 = .05, for anxiety, F (1, 28) =.789, p =.38, n2 = .03, for disgust, F (1, 28) =.147, p =.70, n2 =.01. The only exception was happiness recognition: F (1, 28) = 5.040, p =.03, n2 =.15. Relative to healthy controls, the stroke group had a significantly lower ability of correct recognition of happiness. In addition, the findings showed that there was a tendency for better recognition of negative emotions, such as sadness, anger and anxiexy, in the stroke group compared to healthy controls (Figures 1, 2).

In the next step, the data gathered by the EET administration in the stroke patients were analyzed with repeated measures ANOVA, in which emotion type was the within-subjects factor. The same analysis was made for the data of the "healthy" older adult group. These analyses revealed that emotion type was a significant main effect within each group: Group A: Stroke patients, F (6, 9) = 3.38, p = .05, $\eta 2$ = .69; Group B: "Healthy" older adults, F (6, 9) = 11.92, p = .001, $\eta 2$ = .88. In terms of the pattern of the effects in Group A (Figure 1), stroke patients had their main difficulty in the recognition of non-emotional displays (neutral condition), which was followed by the

recognition of disgust. Inversely, their greater performance was in recognition of hapinness, followed by sadness (Figure 1). Happiness recognition was found to differ significantly from disgust recognition, $p < .05$, while sadness recognition was found to be significantly better from the recognition of pleasant surprise, $p < .01$, neutral expression, $p < .05$, and disgust, $p = .01$.

As regards the pattern of the effects in Group B (Figure 2), healthy controls were almost excellent in happiness recognition, which was followed by recognition of pleasant surprise and sadness. On the other side, the most difficult conditions for them were anxiety decoding and discrimination of non-emotional displays (neutral condition) (Figure 2). In this group, happiness recognition was found to significantly differ from the recognition of all the other emotions and neutral expression ($p < .001$, for the difference with disgust recognition: $p < .01$), except from pleasant surprise decoding.

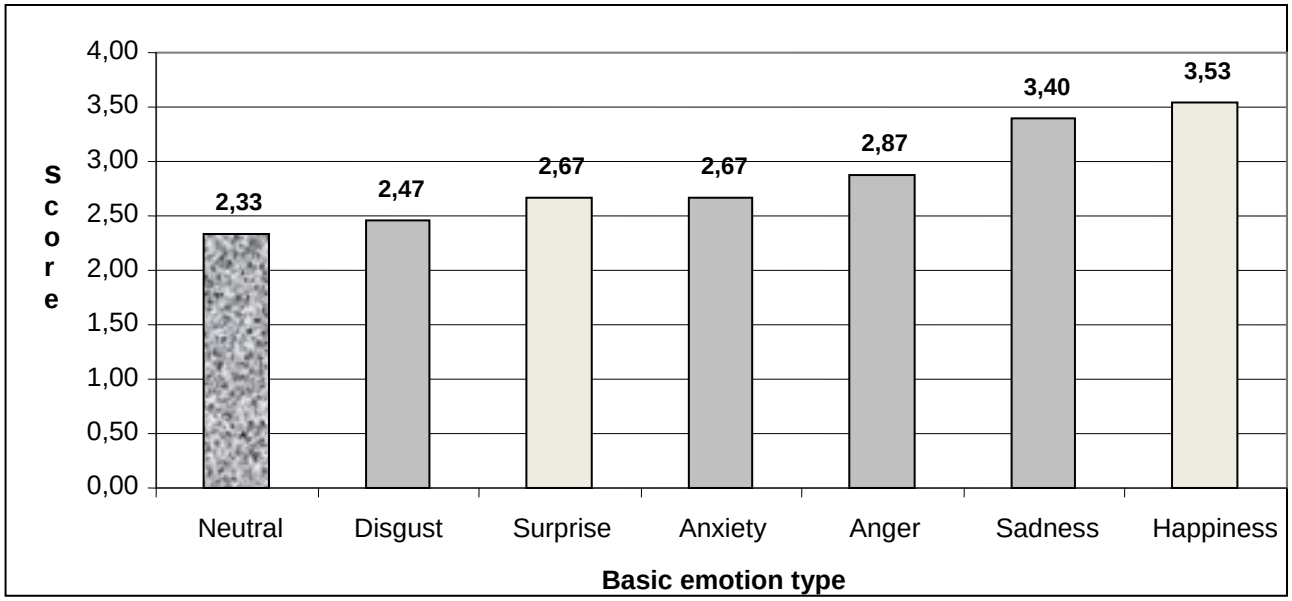

Figure 1. Decoding of basic emotions from dynamic visual cues in older adult stroke patients

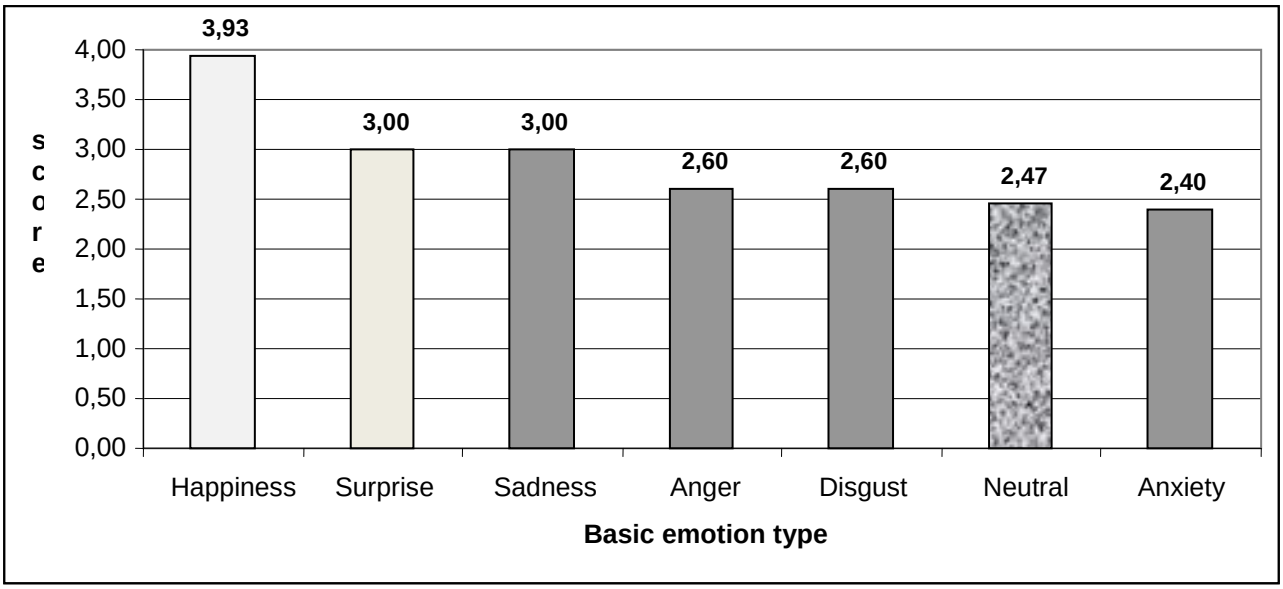

Figure 2. Decoding of basic emotions from dynamic visual cues in "healthy" older adults

Discussion

This study aimed to assess the ability of emotion recognition in older adult stroke patients using dynamic, complex, and naturalistic emotional displays. The first hypothesis formulated was that stroke patients would not recognize dynamic visual displays as well as "healthy" older adults, due to their possibly diminished cognitive resources (Hypothesis 1). This hypothesis was not confirmed, as the two groups of participants did not differ significantly in

basic emotions' recognition, with the exception of happiness decoding. Hence, it seems that basic emotion recognition is resistant to brain damage, and this may be explained by the relatively primitive and instinctive "nature" of this "social skill" [1, 12].

The second hypothesis of this study was that stroke patients would have difficulties in recognizing positively-valenced emotions and especially, happiness, in sharp contrast to the "healthy" older adult participants who were expected to display an excellent performance on happiness recognition (Hypothesis 2). Consistent with our predictions, the results revealed quite clearly that the ability of the older adult stroke group to successfully recognize the emotion of happiness was diminished compared to their "healthy" counterparts, despite the fact that their score on happiness recognition was still very high (see Figure 1). Inversely, relatively to healthy controls, the stroke group was found to display, in terms of a tendency, a higher-level ability to recognize three negatively-valenced emotions, namely anger, anxiety, and sadness. Hence, the current findings seem to confirm mainly the theoretical account of older adults' reversion of the "positivity effect" to an "automatic negativity bias", when circumstances do not allow to devote considerable amount of cognitive control to regulation [4].

In detail, Socioemotional Selectivity Theory offers a motivational explanation, according to which older adults can experience emotional enhancement to the extent that they are capable of exerting cognitive control [29, 30]. A number of studies suggest that wellbeing in older adults is influenced by contextual demands on cognitive processing. In fact, these studies show that only when situations allow for the implementation of control strategies can the wellbeing of older adults be enhanced by cognitive control. However, older adults do not always have access to sufficient cognitive resources for emotional goal implementation (e.g., when they have to complete a concurrent goal-irrelevant task). Interestingly, when older adults' cognitive resources are constrained, they sometimes show a negativity bias in information processing. In recent studies, unlike older control participants, older adults in divided attention conditions were negatively biased when process emotional material in memory and visual attention tasks [31, 32]. Another empirical work [19] suggests that emotion regulation requires cognitive resources, and when processing constraints prohibit the use of effortful goal-related strategies, older adults cannot effectively enhance their wellbeing through cognitive control. Gross [33, 34] outlines common strategies people use to down-regulate their affect when presented with negative material, including selecting a situation by its expected emotional outcome, modifying the emotional impact or meaning of a situation, focusing on selected aspects of a situation, and altering an ongoing emotional response. All these methods of controlling emotions require self-initiated cognitive processing – in other words, executive functioning. From the cognitive neuroscientific standpoint, this cognitive control recruitment can be explained by evidence according to which in "healthy" older adults, age is associated with reduced amygdala activation in response to negative stimuli. This coincides with enchanced activation in the anterior cingulate cortex and the prefrontal cortex. In other words, based primarily on neuroimaging findings, it could be supported that emotion regulation - related brain structures will activate when older adults encounter negative information. Inversely, greater amygdala activation seems to be experienced by "healthy" older adults in response to positive stimuli [4, 31-34].

In the present study, the stroke group had a significantly lower score in MMSE, an indication of a lower-level of cognitive resources, and it might be proposed therefore that the tendency for better recognition of emotions such as anger or sadness is due to the cognitive deficits caused by the stroke. Controlling emotions through cognitive processing requires both the appraisal of affective information [35] and the alignment of cognition with emotional goals [31, 32]. These two criteria require, as already mentioned, processes dependent on the amygdala, prefrontal cortex, and the anterior cingulate [36, 37]. The amygdala is especially useful in detecting emotionally intense material [46] and providing rapid responses to emotional information [38]. It is also necessary for implementing emotion regulation strategies because the affective value of information must be known before goal-directed processing can take place [38]. However, goal-directed processing needs prefrontal cortex and anterior cingulate activation. Even though the accurate location of the brain damage was not taken under account in this study it is possible that the stroke patients - participants had specific difficulties in emotion recognition due to such brain leisures.

Another explanation for these results might be the finding that "healthy" older adults had a higher likelihood of reporting the perception of happiness in faces when being in a positive mood, and a lower likelihood when being in a negative mood [39]. Reduced cognitive resources may have let older adults to rely stronger on other sources of information, such as their current mood, supporting the notion of a heuristic (mood-as-information) processing strategy. Such an explanation could be used, not only to interpret happiness recognition difference in the two groups of this study, but also the high level of stoke patients' performance on sadness recognition as well as their relatively good performance on anxiety decoding, in terms of a tendency. Furthermore, the generally low performance of both groups on disgust decoding could be also interpreted on the basis of a broader experience-related affect of the participants. According to a previous study, disgust decoding from dynamic visual cues is statistically "biased" against adults with lower education. This means that less educated adults' 'lower' ability to decode revulsion or disgust might be influenced by factors different from those affecting disgust recognition in more educated people [4]. In other words, older adult participants in this study (both "healthy" and stroke patients) were not so able to recognize disgust, compared to other negatively-valenced emotions, due to their relatively low educational level. On the other hand, neutrality discrimination, as assessed by the EET, seems to be one of the most difficult tasks for all older adults. Given that McDonald et al. (2006) indicate that neutral expressions included in the EET are the most difficult to interpret because of their strongly ambiguous nature, older adults' performance seems to rather reflect a methodological issue [26, 27].

In line with the aforementioned interpretations, Labouvie-Vief and Medler's (2002) [40] developmental model of self-regulation in adulthood distinguishes between two affect regulation strategies: affect optimization and cognitive-affective complexity. The former has to do with the emotional experience [41]. The latter refers to the conceptual representation and understanding of the emotional experience, which reflects the role of cognition in affect regulation. Based on findings of cognitive and emotional aging, Labouvie-Vief argues that these two strategies of emotion regulation display different aging trajectories, with the ability to optimize affect remarkably improving but conceptual understanding of emotion slightly declining as adults move from middle to old age. Phillips and colleagues (2006) focus their attention on executive functioning, deficits in which have been found as a result of aging and positive and negative mood states. These findings suggests impaired executive functioning of older adults in both positive and negative mood state, possibly because mood interfered with their working memory capacity [41].This might support a more generalized cognitive dysfunction rather than specific emotion deficit and on this basis further research is needed in which the aspects of experienced mood and the perception of emotional expression should be taken under account.

Moreover, according to neuropsychological theories of emotion recognition, older adults' worsening emotion recognition performance stems from the decline of the brain and, especially, of discrete brain regions important for the processing of discrete emotions [30, 42]. This approach could explain the differential performance of both groups and especially of stroke patients, as regards happiness and pleasant surprise decoding. As a previous study showed, lifespan trajectory may not be the same for every positively-valenced emotion. The emotion of surprise is characterized by definition by unpredictability and unexpectedness. Thus, surprise decoding, even if surprise is pleasant (that is positively-valenced), may require the activation of brain regions related to uncertainty processing [4, 43-47]. In such a case, positive emotional valence cannot function as a compensatory mechanism for declines in these brain regions. Generally speaking, more research is needed for specific emotions with complex characteristics such as surprise, especially in pathological aging.

Nevertheless, relying on a single theoretical approach for age or/and related to brain pathology differences in emotion decoding from visual cues is simplistic and the results shown above are in line with this view. In sum, evidence presented so far indicates that the primary affective appraisal structure (amygdala) seems to remain stable while emotion control regions decline with age [48-50]. Yet even with age-related deterioration to regulation structures, "healthy" older adults can promote their emotional wellbeing by recruiting additional cognitive resources to implement their regulation goals, while stroke patients cannot, at least to the same extent and mainly as regards the specific emotion of happiness.

Limitations and future directions

Our research findings must be interpreted with several limitations in mind. First of all, even though we knew in which hemisphere the stroke took place, we had no information about the specific region and the extent of the damage. The restricted nature of the sample should be noted, especially with regard to the confounding of age and educational level, as well as to the number of participants in each group. An additional limitation is the cross-sectional design of the study. It is unknown if the same pattern of results would be obtained if the stroke patients were repeatedly measured at different times. Generally speaking, more rigorous designs and methods are needed to examine the effects of normal and pathological aging on emotion recognition. However, it is an advantage of the present study that emotion recognition was not assessed in self-report or by the means of tests including static cues but with an ecologically valid, dynamic tool. On the other hand, stroke patient participants were all recruited from the programme "Help at Home" which helps poor and abandoned older adults and, due to this, they may experience more negative emotions than their more privileged counterparts. So, they may also identify more easily negative than positive emotions, compared to them.

Results from this study would be also strengthened by exploring systematically the cognitive and perceptual components of emotion recognition in cognitively healthy and unhealthy older adults, through the use of a comprehensive neuropsychological battery and neuroimaging, through manipulations in order to change the cognitive or perceptual load of emotion recognition tasks as well as by examining multiple varieties of emotion tracking.

The authors declare that they have no conflicts of interest.

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Can MCI patients classified as SNAP or PART by their CSF profile be differentiated from prodromal AD patients by neuropsychological assessment?

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Abstract

MCI patients can be classified according to the NIA-AA criteria for Alzheimer's disease (AD) into different risk groups for conversion to AD (high, or intermediate likelihood, and uninformative) based on their biomarker profile [1]. In our study we took into account this classification system and integrated additional literature data about the "uninformative" profiles ending up to the following groups of risk of AD conversion: low AD risk including Suspected Non-Alzheimer's Disease Pathology (SNAP), as well as Primary Age-Related Tauopathy (PART), and high risk including prodromal AD [2] [3]. We divided a consecutive clinical sample of 65 MCI patients from a memory clinic into these three groups based on their CSF biomarker values (amyloid pathology: Aβ1-42 – neurodegeneration: p-tau, and total tau) with the aim to investigate whether they differ in terms of cognitive performance, as measured by the CERAD neuropsychological battery (verbal learning, episodic memory, verbal fluency, constructive ability) and the Trail Making Test (TMT) parts A and B (visual scanning, working memory). A statistically significant difference was detected on constructive ability between SNAP and prodromal AD. No further significant differences on cognition emerged among the groups. We attribute the latter finding to our small sample. Alternatively, we propose that CERAD and TMT may not be appropriate to discriminate the fine cognitive differences among prodromal AD, SNAP, and PART and that other psychometric measures, such as the FCSRT [4] should probably be used for these patients. Future research needs to further investigate the cognitive profile of SNAP and PART and determine to which extent this differs from the one in prodromal AD.

Introduction

The diagnosis of Alzheimer's Disease and its differential diagnosis from other types of dementia is a difficult task, as a wide range of information needs to be taken into account, including history, clinical neurological and neuropsychological data, neuroimaging data (e.g. brain atrophy), as well as additional biomarker indices like genotype, and cerebrospinal fluid (CSF) protein profile. A recentsystematic approachto define guidelines in diagnosing AD was conducted by theNational Institute on Aging-Alzheimer's Association (NIA-AA). Itsrecommendations incorporate CSF biomarkers, and classify patients into probable AD, or possible AD, while some patient profiles may be uninformative [1, 5]. NIA-AA also classified patients with mild cognitive impairment (MCI) intorisk groups in terms of high, intermediate, or low likelihood of MCI conversion to AD.[6]

New research data show that there are patients with cognitive complaints and positive biomarkers of neuronal injury, including hippocampal atrophy and cortical hypometabolism, but no amyloid pathology, a condition described as Suspected non-Alzheimer's disease pathology – SNAP[3]. Craryand colleagues (2014) also introduced the term Primary age-related tauopathy (PART) to refer to a condition characterised by medial temporal lobe atrophy and pathological CSF tau levels in the absence of amyloidosis.Yet, there is currently controversy as to whether PART belongs to a continuum of neurodegeneration that takes place naturally in the frame of normal ageing or it is an early process anda component of Alzheimer's disease [7].Therefore, PART needs to be defined in further detail. Moreover, it is necessary to betterdiscriminate PART from SNAP in terms of additional clinical and neuropsychological traits, as well as pattern of neurodegeneration [8].

The purpose of this study was tooutlinethe neuropsychological profile of MCI patients with a typical SNAP, or PART CSF profile, and to investigate whether, andto which extent they differfrom one another and from prodromal-AD patients in terms of cognitive abilities. Given the evidenced relationship of CSF biomarkers to cognitive performance, we hypothesised that CSF signature would differentiate SNAP and PART patients from those with prodromal AD.

Methods

Sixty-five patients of a memory clinic, diagnosed with MCI were included in the study. The patients did not differ in terms of age and Mini Mental-state Examination (MMSE) score (see Table 1).Lumbar puncture took place in order for CSF to be collectedand the levels of biomarkers designatingamyloidosis(Aβ1-42), and neurodegeneration (p-tau, t-tau) to be identified. According to the CSF profile, patients were classifiedeither asSNAP(normal Aβ1-42

values, and normal p-tau, normal t-tau values, n = 22), or asPART (normal Aβ1-42 values, and normal p-tau, abnormal t-tau values or inverse, n = 16). A third group of patients with prodromal AD (n = 27) and a typical-AD CSF profile (abnormal Aβ1-42 values, and abnormal p-tau, abnormal t-tau values) was also included to serve as a comparison. Cognitive performance of all patients was assessed in terms of verbal learning, episodic memory, verbal fluency, and constructive ability (CERAD neuropsychological battery), as well as visual scanning, and working memory (Trail Making Test –TMT, parts A and B). A series of univariate analyses of variance were conducted to compare the groups on their cognitive performance.

Table 1: Mean values of the sample's age, MMSE score and CSF biomarkers

Patient group	Group Size	Age (±SD)	Gender ratio (male/female)	MMSE	CSF profile $A\beta_{1-42}$	p-tau	t-tau
SNAP	22	67.3 (±10)	17/5	27	859.4	42.3	191.3
PART	16	70.6 (±5.9)	9/7	27	707.3	83.2	392.9
Prodromal AD	27	70.3 (±8.4)	13/14	27	303	81.9	441.9

Patients did not differ significantly in terms of age and MMSE score. CSF values are abnormalinprodromal-ADpatients, but normal in SNAP. Only tau indices are abnormal in PART.

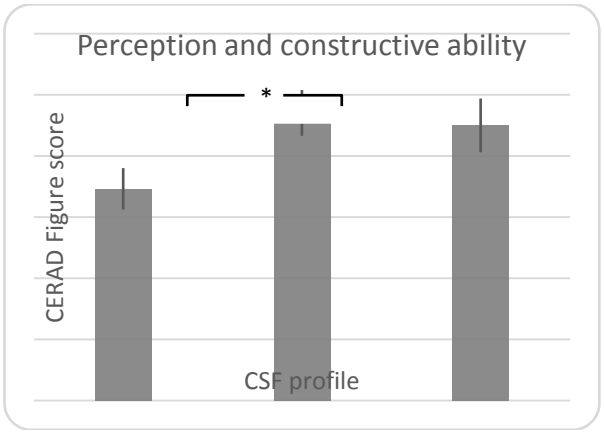
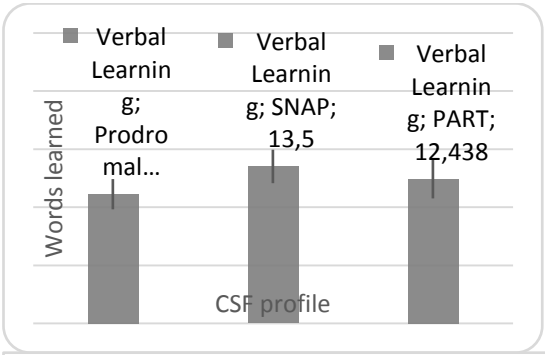
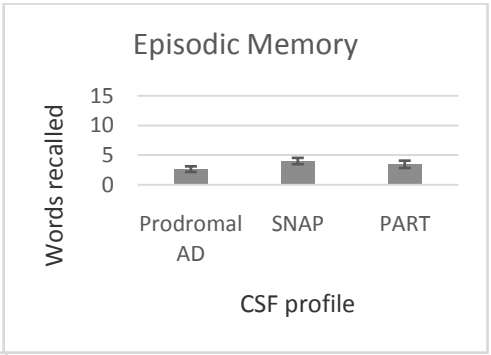


Figure 1: Significant difference in constructive ability between SNAPand prodromal AD (*p < .05). SNAP patients demonstrated a better performance.





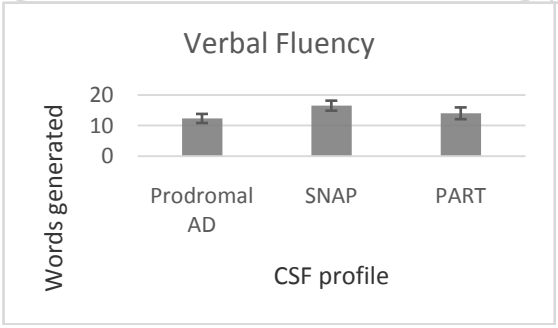


Figure 2: No significant differences in verbal learning, episodic memory, or verbal fluencyamong, SNAP, PART, and prodromal-AD patients (p > .05). Scores of SNAP and PART patients are higher than those ofprodromal-AD patients.

Cognitive tests	Patient groups			Maximum score
CERAD	Prodromal AD	SNAP	PART	
Wordlist (verbal learning)	11.1	13.5	12.4	30
Wordlist (delayed recall)	2.6	4.0	3.4	10
Verbal fluency	12.4	16.5	14.1	-
Figure	6.9	9.4	9.0	11
TMT				
Part A	50.7	60.4	78.4	-
Part B	160.4	171.5	211.1	-

Table 2: Mean scores of all groups on the CERAD subtests and TMT.In spite of absence of statistical significance, SNAP and PART patients performed better than prodromal AD patients on the CERAD subtests, but worse on both TMT parts.

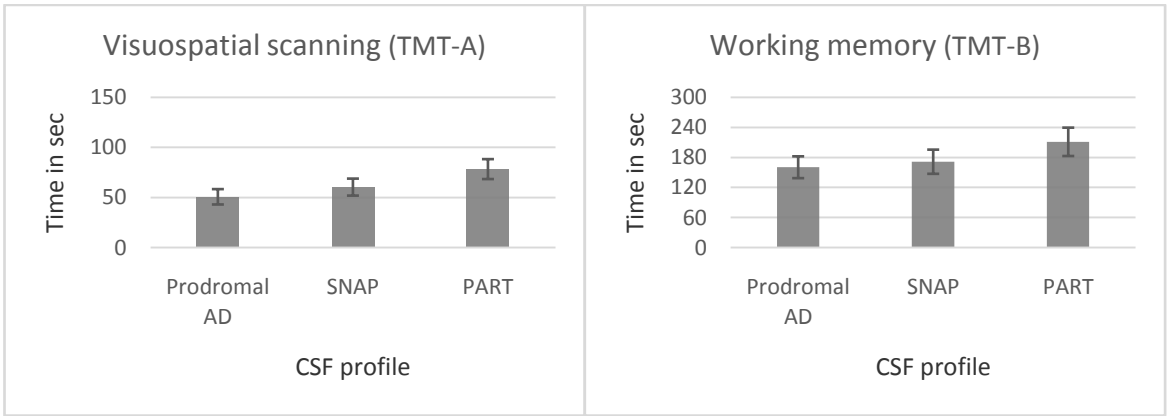


Figure 3: No significant difference in visual scanning and working memory among the three groups (p > .05). SNAP and PART patients achieved higher time-scores than prodromal-AD patients.

Results

Cognitive performance on CERAD's constructive-ability subtest was found to significantly differ (p<.05, η^2 = 0.101) between SNAP patients and prodromal AD (see Figure 1). PART patients' performance did not differ significantly from that of either group (p>.05).

No further statistically significantdifferences onthe rest of the CERAD subtests (verbal learning,episodic memory, and verbal fluency) emerged (p> .05) among the groups (Figure 2). However, SNAP and PART patients achieved betterscores than prodromal AD patients (Table 2). Regarding visual scanning, and working memorypatients with SNAP and PART demonstrated poorer performancethan patients with prodromal AD in both TMT parts (Figure 3). This effect, however, did not reach statistical significance (p> .05).

Discussion

We found that MCIpatients with a typical SNAP, or a typical PART CSF profile can be discriminated from patientswith prodromal AD only in terms of perception and constructive ability, but not in verbal learning, episodic memory, or verbal fluency, when assessed with the CERAD battery. Despite absence of statistical significance in the latter CERAD subtests, SNAP and PART patients performed in them better than patients with prodromal AD.Interestingly, SNAP and PART patientsdemonstrated poorer performance in TMT (Parts A and B) compared to prodromal AD, with the PART patients achievingworse time-scores than SNAP. Yet, the difference among the three

groups did not reach statistical significance. Given the above described tendencies, we attribute the lack of significant differences in verbal learning, episodic memory, verbal fluency, as well as visual scanning and working memory to methodological parameters including small sample size. Alternatively, we propose that CERAD and TMT may not be appropriate to discriminate the fine cognitive differences among SNAP, PART, andprodromal AD,and that other psychometric measures, such as the FCSRT[4] should probably be used for these patients. The finding that SNAP and PART patients demonstrated a poorer performance than prodromal AD in visual scanning and working memory should be further investigated with additional tests. Future researchneeds to focus on clarifying the cognitive profile of SNAP and PARTandto determine to which extent such patients differ from one another and from prodromal AD.

Acknowledgements

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The authors declare that they have no conflicts of interest.

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Abstracts

Foreign language learning and special educational needs: A cause for anxiety

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Abstract

Foreign language proficiency entails the development of aptitude and expertise in a linguistic code which could bear some resemblance to the native one or none at all. It is a complex and complicated process which requires the activation and involvement of various cognitive functions. The three layers of native language coding, i.e. the phonological, syntactic, and semantic ones, along with meta-cognitive awareness skills have been deemed as catalysts for successful foreign language acquisition. Particularly critical appears to be the role of rapid reading skills, and of phonological short-term memory. Vocabulary learning has been found to strengthen the connection between phonological short-term memory and foreign language learning. The accessibility of the foreign linguistic code is further conditioned by its level of transparency. The novel linguistic items may be processed more easily if they resemble the native sound system. The similarity of sound structures could ultimately increase listening comprehension skills. Consequently, if any of the aforementioned systems is defective, foreign language learning becomes a cumbersome task for the learner. Even if potential learning difficulties are latent in nature in a speaker's native language, when emerged in the process of foreign language learning, such deficiencies are almost bound to surface. Hence the feeling of anxiety many special educational needs students develop towards foreign language learning.

Homocysteine and leukoencephalopathy. Correlation review

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Abstract

The goal of this review/study is to examine the toxic results of Hyperhomocysteinemia (Hhcy); especially the association between Hyperhomocysteinemia and Leukoencephalopathy. For this reason, the database PubMed was searched for English language publications with the key words "Homocysteine" and "Leukoencephalopathy". According to Biochemistry there are 5 main reasons inducing Hhcy: 1) Deficiency of Methionine Synthase, 2) Deficiency of MTHFR (MTHF Reductase), 3) Deficiency of B12, 4) Deficiency of Folic Acid and 5) Deficiency of enzymes in the synthesis pathway of cysteine (e.g. b-synthase cystathionine). Nowadays, it is widely accepted that there is a high degree of correlation between Hhcy and Vascular Disease, Alzheimer Disease, Cerebrovascular Disease and other neuropsychiatric disorders. As new researches indicate, there is a possible association between Hhcy and Leukoencephalopathy, as it has been noticed in patients with CADASIL. Even more, Leukoencephalopathy has been noticed in people with one of the above 5 metabolism disorders that also had Hhcy. All of these disease associations are thought to be interrelated via increased homocysteine and S-adenosylhomocysteine and subsequent hypomethylation of numerous substances, including DNA and proteins, that render vascular structures and neurons more susceptible to damage and apoptosis. Providing the nutritional cofactors for proper functioning of the methionine cycle may improve methylation and protect the brain from damage. Furthermore, hyperhomocysteinemia is a strong independent risk factor for SVE (subcortical vascular encephalopathy). Last but not least, Diabetes Mellitus II affects tHcy and FOL values, suggesting a paradoxical phenomenon when diabetes is superimposed to dementias.

Transcranial Direct Current Stimulation (tDCS) as a cognitive enhancement therapy in Mild Cognitive Impairment and dementia

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Abstract
Transcranial direct current stimulation (tDCS) of different cerebral regions, has resulted in modifications of mood, cognitive and behavioral functions in normal individuals and also different pathological conditions with beneficial network effects. Decades ago the impact of weak electrical currents on neuronal function has been described but still remained with lack of clinical usage. The pharmacological therapy of dementias and Alzheimer's disease (AD) is limited and accompanied by drug side effects. It has been shown that tDCS improves working and visual recognition memory in humans and object-recognition learning in the elderly. AD's neurobiological mechanisms induce changes in neuronal activity and the cerebral blood flow (CBF), synaptic dysregulation from ß-amyloid peptide and tau protein accumulation, and alteration of neuromodulation via degenerated modulatory amine transmitter systems, brain oscillations, and changes in network connectivity. Various studies showed that tDCS is capable to modulate neuronal activity and alter cerebral blood flow (CBF), oscillatory brain activity and functional connectivity patterns in the brain. It has also synaptic and non-synaptic after-effects and can modify neurotransmitters polarity-dependently. It thus is reasonable to use tDCS as a therapeutic instrument in AD as it improves cognitive function in manner based on a disease mechanism. There is evidence that tDCS enhances memory in cognitive rehabilitation of depressive patients and is useful in treatment of different neuropsychological disorders including anxiety disorders, Parkinson's disease, stroke, insomnia, chronic pain and migraine. Alternative therapeutic strategies such as tDCS which has shown not only no side effects but benefits, may be considered in treatment of mild cognitive impairment and dementias. Cerebral stimulation with weak direct current is a promising tool in clinical neuroscience.

Brainbanks: How familiar are the medical students with these biobanks?

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Abstract
Objective: Brainbanks have demonstrated an important role in Europe over the previous century, while Panhellenic Brainbank of Neurological Diseases was founded in Thessaloniki just in November of 2013. This promising attempt should be recognized by young scientists in order to contribute to research in Greece. However, many questions arise about how familiar the Greek medical students are with this type of biobanks. **Subjects and methods:** A questionnaire was created, targeting exclusively to medical students. They were asked if they were aware of the existence of brainbanks, how these biobanks work, what their significance in research is, and furthermore the ethical dilemmas which may arise. **Results:** 226 medical students from all the medical schools in Greece have answered the questionnaire. The statistical evaluation of the data revealed that 45,6% know what a brainbank is, but only 14,6% are aware of the existence of Panhellenic Biobank of Neurological Diseases. 90,3% consider the donation of brain not to be an immoral act and 71,2% reckon that brainbanks contribute to the future of research from "much" to "very much". **Conclusions:** The results of this particular study seem to be hopeful for the future, but, we should not be tranquilized. It would probably be beneficial for the medical students to be sufficiently informed not only about the function and the importance of these biobanks, but also about the ethical and legal issues that arise, so that they will be capable of spreading and contributing to the development of brainbanks.

A classification and comparative study of European Biobanks

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Abstract
The term “biobank” denotes a collection of samples brought together for use in research. These repositories of biological specimens have witnessed an exponential increase in their number, resulting in confusion regarding the quality of their infrastructure and the type of tissue collected. In addition, taking into account their unequal geographical allocation, problems arise in the interchange of material between scientific teams and these organizations. In the current study, we have examined a statistical sample of 59 biobanks established in 12 European countries, collecting data from 2 networks; Biobanking and BioMolecular resources Research Infrastructure (BBMRI) and EuroBioBank. Our set of entities under study consists of biobanks with a considerable scientific outreach, defined by the number of recent publications in which they had a significant contribution. Thus, we aim to provide a synopsis of the key characteristics of a biobank, which can be subsumed under the following categories: type, research focus, collected biological samples and location. Through analysis, the most frequent types of biomaterial used in research projects have been determined. In addition, a positive correlation has been estimated between the number of biobanks focusing in one disease group and their number of publications, indicating a possible relevance between progress in one field and the number of biobanks providing samples for utilization.

The involvement of aging in the development of Alzheimer’s disease

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Abstract
Alzheimer’s disease (AD) is a chronic neurodegenerative disease and the most common cause of dementia. Although a wide spectrum of genetic and environmental causes have been linked to the development of AD, aging remains the major established risk factor. Several studies have reported anatomical and cytological resemblances between the aged brain and AD. The current paper aims to summarize these connective elements from a both macroscopic and microscopic perspective. In addition, it presents age-specific rates of sporadic AD as well as similarities between the early-onset type and the theories of aging. However, despite this correlation, the mechanisms of the aging process associated with the appearance of AD remain unspecified. Moreover, latest evidence demonstrates that senescent cells increase with advancing age. Cellular senescence can be defined as a permanent cell-cycle arrest initiated by various endogenous and exogenous stimuli. In this review, possible physiological pathways between cellular senescence and the emergence of sporadic AD are examined. In detail, recent analysis proposes the contribution of (1) oxidative-stress induced neural senescence (2) replicative senescence undergone by microglial cells (3) astrocyte senescence and (4) senescence of the cerebrovascular system, to the distinct pathological features of AD. Understanding the aspects of aging, both on a systemic and intracellular level, is expected to shed further light on current prognostic and therapeutic approaches for AD.

Measuring social cognition and cognitive control in Mild Cognitive Impairment: comparison with cognitively healthy older adults

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Abstract

Social cognition is the sum of the abilities that allow individuals to interact with each other. In fact, in order to perceive both the self and the other, a person has to represent their mental states and infer differences between them. All the processes needed for these representations are included under the umbrella concept of Theory of Mind (ToM). Cognitive control (Cc) is defined as self-initiated cognitive processing which is mainly dependent on the prefrontal brain region. It includes a series of higher-order cognitive functions, known as executive functions. Recent research on Mild Cognitive Impairment (MCI) tends to support that both ToM and Cc display some decrements in MCI patients, compared to healthy peers. However, the picture is not clear enough. The present study aimed at examining the level of ToM and Cc abilities as well as their relationships in older adults diagnosed with MCI. The sample comprised a total of 42 older adults (age: > 65 years), who were distributed in three groups: the MCI patients (group 1: n = 15), the cognitively healthy older adults having risk factors for cardiovascular disease development (group 2: n = 15), and the healthy controls (group 3: n = 12). The tasks administered were a) a ToM test measuring nonliteral language (sarcasm) understanding, b) a test examining emotion recognition, c) four Cc tasks measuring inhibition, switching and planning. Data processing is made using ANOVA's to find quantitative differences, while multi-group path analysis is used to reveal qualitative differences in ToM and Cc abilities among the groups. The directed relationships among ToM and Cc are shown in path models confirmed. Hence, based on the findings, a profile of the ToM and Cc abilities in MCI will be created, that could be used as a tool for differentiating MCI patients from cognitively healthy peers.

Social cognition and cognitive control in Alzheimer's Disease: examining the differences between older adults diagnosed with MCI and AD

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Abstract

"Theory of Mind (ToM)" reasoning, defined as the ability to understand mental states of the other people, is crucial in social interactions. Recent theories suggest that taking someone's mental perspective requires two distinct processes: inferring someone's mental state and inhibiting one's own mental state. In the abovementioned processes specific cognitive control (Cc) abilities may be involved. Cognitive control is defined as self-initiated cognitive processing which includes a series of higher-order cognitive functions, known as executive functions. Research on Alzheimer's Disease (AD) supports that AD patients have a predominant deficit in inferring someone's mental state as belief. However, it is not clear if this specific deficit is associated with Cc decrements besides deficits in working memory functioning. In this vein, the present study aimed at examining the level of ToM reasoning as nonliteral language understanding, and its relationships with specific Cc abilities in older adults diagnosed with AD. The sample comprised a total of 45 older adults (age: > 65 years), who were distributed in three groups: the AD patients (group 1: n = 15), the MCI patients (group 2: n = 15), and the cognitively healthy older adults having risk factors for cardiovascular disease development (group 3: n = 15). The three groups were matched for age, gender, and educational level. The tasks administered were a) a ToM test measuring nonliteral language (sarcasm) understanding, b) a test examining emotion recognition, c) four Cc tasks measuring inhibition, switching and planning. The level of ToM reasoning and the causal relationships between ToM and Cc are shown in recursive and non-recursive path models confirmed for the groups, respectively. Hence, based on the findings, the level of ToM as nonliteral language understanding and its dependence on specific Cc abilities in AD will be revealed and differentiated from those of MCI patients and healthy elderly.

Attitudes and understandings of the grandchildren of dementia patients

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Abstract

Dementia is a clinical syndrome characterized by significant cognitive impairment burdening gradually autonomy and independence. With life expectancy increasing, the cases of dementia in elderly population increase as well. With the increase of dementia cases, the numbers of family members - who experience the disease's symptoms daily by taking care of the patient - also increase. Such members of the extended family are the grandchildren of dementia patients. Aim: Grandchildren (n=50, 14-21 years old) and their mothers (n=40, 40-65 years old) participated in this study. The aim of this research is to explore the attitudes and understandings of the grandchildren of dementia patients regarding health; the disease; their relationship with their grandparents; and their emotional state. The same factors are examined with regards to the children's mothers. Finally we investigate the emotional interaction between grandchildren and mothers. Method: For the needs of this research we used the Burden Interview scale (Zarit) for the mothers, while for the grandchildren we constructed a questionnaire examining the relationship satisfaction; the quality and frequency of contact with grandparents; and the children's emotional state. Results: Grandchildren and their mothers living with the patient experience a greater emotional impact and burden than those who do not. To this substantially contributes the clinical state of the patient and the nature of their relationship with her/him. There is a positive correlation between the emotional state of the grandchildren and the emotional burden of the mothers. Regarding their own health assessment there is correlation with the sex of the grandchildren. Conclusion: Grandchildren understand and accept the symptoms and the health state of their grandparents. There is a particular emotional interaction between parent and child.

Use it more and keep it alive: Longitudinal cognitive training in Mild Cognitive Impairment

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Abstract

Background: Cognitive training may optimize the cognitive functioning of MCI patients. However, further studies are needed to examine the long-term effectiveness of cognitive training. **Aim:** Patients with amnesic and multi-domain Mild Cognitive Impairment were followed up after two years of cognitive training. **Methods:** One hundred and six patients were classified in two groups, experimental and control, matched in age, gender, education, cognitive, and functional performance. Seventy four attended 32 weekly sessions of executive function training, during one year. Forty one out of them attended 34 weekly sessions for one more year. The control group (N=32) continued the regular daily activities. Neuropsychological assessment was performed at baseline, one and two years later. **Results:** At the end of the first year, the experimental group (N=74) had better performance than controls in verbal ($p \leq 0.031$) and visual memory ($p = .005$), executive function ($p \leq 0.008$), IADL ($p \leq 0 .025$), global cognitive ($p=0.020$) and functional performance ($p=0.003$). At the two years follow up, the participants with two years of training had better performance than controls in verbal ($p \leq 0.005$) and visual memory ($p=0.001$), executive function ($p \leq 0.012$), IADL ($p \leq 0.004$), and global cognitive and functional performance ($p=0.000$). The participants with two years of training had better performance than participants with one year of training in verbal ($p=0.007$) and visual memory ($p=0.007$), executive function ($p \leq 0.009$), IADL ($p=0.009$), and global functional performance ($p=0.000$). The participants with one year of training had better performance than controls, in executive function ($p \leq 0.013$), global cognitive ($p=0.016$) and functional performance ($p=0.009$). **Conclusion:** Two years of cognitive training is more beneficial for MCI patients, than one year of training or no training.

Care of patient with dementia: Will or Duty

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Abstract

The lasts decades the aging of population has been a dramatic rise in the rate of Alzheimer's disease and generally in dementia. In the severe dementia, patients become depended due to the degeneration of the brain. The other members of the family and other caregivers are responsible for difficult decisions concerning the care of patient. May caregivers be called to decide about a surgery or a hospitalization? Could they suggest a painful treatment for a patient who cannot understand its purpose and is close to the end of life? The decision about artificial nutrition and hydration, the technical support of breathing etc., is among the decisions the family and physicians must make. Despite the fact that there is no law that forbids or forces the use of these technical supports, the family often has to make a decision, to face the dilemma to use or not any technical support. The main question is how somebody can help a caregiver to make a compassionate, ethical and logical decision for the care of his patient. Ideally, this decision has to reflect the virtues of the patient and derive from the main purpose of care. Unfortunately, what patient want and prefer cannot become known to the caregivers and the purpose of care, like the extension of life that promote the independence or the palliative care, cannot in fact exist. During the care of patient suffering from severe dementia there are many dilemmas that become by the conflict of I Want and I Must. These dilemmas are experienced also by the family members and the health professionals.

Social Work in the years of economic crisis

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Abstract

The economic crisis in our country is sharpened. Unemployment and population groups that are unable to cope with the basic requirements of their daily life are in continuous increase. Malnutrition, poor housing and living conditions, depression, suicide attempts, health problems in children and adolescents, violence, delinquency, environmental problems, social inequalities, violations of human rights, economic migration is some of the parameters that are vertical percentage rise and deterioration. At the same time demand on education, health and social care is increasing and uncertainty and insecurity about the future are amplified. The economic crisis and the new situation of course has affected the lives of patients with dementia and their families. Unemployment, lack of financial resources to meet their needs, has affected both the psychology of these people and their standard of living. They can enjoy less help from people who previously could pay, choosing to introduce their relatives to clinics that have contracts with insurance providers regardless of the conditions and generally their decisions now are taken based on economic paremeters.

Oral health and dementia during Economic Crisis

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Abstract

Oral health of patients suffering from Alzheimer disease or any other type of dementia is indissolubly connected to their total health condition. Dental indexes are often used in research when the quality of living standards is being evaluated. During economic crisis eras, the living standards deteriorate and the way of living changes in multiple levels. A dentist receives a different clinical image in everyday medical practice with patients and this is something that shows in dental measuring as well. That picture is even clearer with patients suffering from dementia.. Economic crisis has therefore created a difficulty in acquis ion of the proper medical and cosmetic preparations, it has made access to the dentist difficult for all patients and it has caused a restructuring of priorities for all patients and their families. In Alzheimer Hellas there is a dental department from 2007 up to today, which takes care of patients inside the dental department or at home within the framework of the proper team. Economic crisis has an impact on those patients, apparent in their oral health condition. Oral cavity neglect approaches its levels back in the sixties, when in Greece a significant population section was ignorant in this area. When it comes to patients treated at home, their condition is so critical that even their nutrition status can be affected. It is thus our goal to serve and inform the patients as well as their families for the value of oral hygiene even during difficult times like today.

Mild Cognitive Impairment and visual problems

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Abstract

Visual and hearing impairments which increase with the ageing of population are possible to affect cognitive functions as well as the quality of life of the individual at a significant level. Studies which aim to evaluate the quality of life of the elderly with visual problems reveal that those who suffer have great difficulty in handling everyday activities, high levels of anxiety and consequently low quality of life. Moreover, a wide research field deals with the positive correlation between visual and cognitive impairment as far as the elderly are concerned. An interesting possible implication is that early interventions towards vision correction may reduce the severity of dementia and its associated functional decline even in the case of elderly with low visual acuity levels. Furthermore, the visual and hearing loss together is correlated with bigger cognitive decline than by each one separately. The cognitive performance during the individual's neuropsychological evaluation may be influenced by the level of his/her sensory functions and be underestimated if the sensory problems are not considered. For that reason, it is necessary to discuss the cognitive performance of an elderly woman with macular degeneration and partial hearing loss through her participation in non-pharmaceutical interventions over the years. The organizing of life style through the adaptation of internal memory strategies, the existence of motivation, the personality potential and the participation in outdoor activities are a few of the strategies that have helped the individual maintain a stable cognitive profile over the years and reduce the risk of developing dementia

Mild Cognitive Impairment with behavioral problems

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Abstract

According to the international diagnostic criteria (DSM-5) there are different subtypes of neurocognitive disorders. One of these is the mild or the major frontotemporal neurocognitive disorder, which previously used to be referred to as frontotemporal dementia. For the diagnosis of the mild or major frontotemporal neurocognitive disorder, the following criteria are necessary to be fulfilled. Firstly, there has to be a suspicious beginning and a progressive cognitive deterioration. Secondly, the patient has to develop either language deficits or behavioral disorders, while memory and perceptual abilities are well maintained. The patient who is going to be presented is a 73 year old woman with 6 years of education, diagnosed with mild frontotemporal neurocognitive disorder. Her mental profile demonstrates disorders in cognitive functions and specifically in episodic, verbal and visual memory, whereas the disorders in executive functions seem to be of greater importance. As far as the functionality is concerned, she shows deficits in the complex abilities execution, while she emotionally shows mild anxiety. However, the most important disorder is related to her behavior, as the patient is aggressive, anxious, easily irritated, has lack of suspensions and presents pathological motional behavior. Furthermore she shows addiction to gambling, changes in nutritional habits and lack of interest in her appearance. Finally, she shows partial mental awareness ability, but absent awareness of her behavioral disorders. The patient is not under medication for her mental symptoms neither for the behavioral disorders. However, she is under anxiolytic medication and she participates in cognitive training.

Is Alzheimer's Disease type 3 diabetes?

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Abstract

In recent studies, a correlation has been observed between AD and diabetes mellitus type 2 (DM) another disease that affects over 250 million patients worldwide (4th death cause in USA), as well as other cardiovascular risk factors such as obesity which is highly correlated to DM. Moreover, DM patients have increased risk of developing AD compared to patients without DM. Insulin and insulin-like growth factor type I and II (IGF-I and IGF-II) signaling mechanisms in brains with AD were studied, and it was observed that the expression levels are markedly reduced in AD. Reduced CNS expression of genes encoding insulin, IGF-I, and IGF-II, as well as the insulin and IGF-I receptors, suggests that AD may represent a neuro-endocrine disorder that is closely related to DM. Moreover, DM and AD are characterized by localized amyloid deposits in pancreas and brain respectively that progress during the course of the disease and share pathophysiological similarities. PPAR agonists (such as rosiglitazone and pioglitazone), which are drugs used to treat DM, prevent many of the AD-associated neurodegenerative effects of experimental animal models. Therefore the term 'Diabetes type 3' for AD was introduced. An overview of the current studies on the relationship between AD and DM will be presented.

Theory of Mind in frontotemporal dementia: Theoretical background and clinical implications

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Abstract

Frontotemporal dementia (FTD) is a focal form of dementia, differentiated from other degenerative diseases both clinically and pathologically. Although this type of dementia is the most common after Alzheimer's disease and accounts for up to 20% of cases of dementia affecting people in middle age, diagnosis still remains difficult. The diagnostic difficulty is usually ascribed to FTD's insidious onset and ambiguous clinical features, which may cause confusion with other degenerative diseases or mental disorders. The most prominent symptom is a dramatic alteration in a patient's personality and social attitude, while other cognitive abilities such as perception, spatial skills and memory are relatively spared. It has been suggested that a key mechanism which may interpret several of the abnormalities in interpersonal behavior occurring in the behavioral variant of frontotemporal dementia (bvFTD) is a Theory of Mind (ToM) deficit. ToM is a component of social cognition and refers specifically to the ability to infer other persons' mental states, thoughts and emotions. Recent studies have explored the cerebral substrates of ToM deficits that characterize bvFTD patients. Although there are conflicting reports, there is a significant body of evidence suggesting that medial prefrontal cortex – a region that is affected in the early stages of bvFTD - appears to play a central role in ToM functioning. Furthermore, more complex and sophisticated models about the underlying neural basis of ToM have lately emerged. Research data have provided clinical and neuroimaging evidence to suggest that ToM ability comprises several components which are subserved by distinct cerebral regions. In conclusion, novel findings suggest that impaired ToM components may reflect damage to specific brain regions or networks and highlight the importance of using validated neuropsychological batteries for ToM assessment in order to evaluate the integrity of these regions and contribute to bvFTD early diagnosis.

The added value of HD-EEG recordings in the diagnosis of Alzheimer's disease and Mild cognitive impairment

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder that is characterized by cognitive deficits, problems in activities of daily living, and behavioral disturbances, and consists the most common form of dementia met in western societies. Mild Cognitive Impairment (MCI) is a transitional state in cognitive functions between changes deriving from normal aging and dementia. Worldwide, researchers make lot of effort in order to find sensitive and accurate biomarkers, that will make possible earlier diagnosis and more accurate prognosis for the disease. Electroencephalogram (EEG) has been demonstrated as a reliable tool in dementia research till now. EEG consists an important method of brain electrical activity recording and investigating. Since its invention till nowadays, great technological advances have been applied on EEG equipment, resulting to the dense arrays of electrodes used today. Moreover, the progress of the mathematical analysis of the EEG recordings has led us to new research pathways of brain activity, the brain mapping and the connectivity studies. Despite the fact that EEG is not included in the first line diagnostic procedure of AD and MCI, it has been used in dementia research and diagnosis, the differential diagnosis and the prognosis of the disease progression, as presented in several studies. Recent studies about AD and MCI, using HD- EEG recordings present new and interesting data. Their research value and clinical utility remains a hot research topic regarding AD and MCI.

Event-related potentials in the diagnosis of Alzheimer's disease and Mild Cognitive Impairment: current status and future prospects

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Abstract

Alzheimer's disease (AD) and mild cognitive impairment (MCI) constitute a major public health concern and affect millions of people worldwide. The diagnostic approach and therapeutic management of these disorders may be significantly improved by recent advances in the area of event-related potentials (ERPs). Major research emphasis was placed on the role of ERPs in identifying MCI patients who will later on develop AD, the contribution of ERPs in the differential diagnosis of dementia types, the utility of ERPs for monitoring pharmacological treatment in AD and the correlation between ERPs and the results of neuropsychological testing. In particular, N200 and P300 waves have been widely studied over the last years in patients with dementia. The reviewed evidence suggests that ERPs hold promise as a useful electrophysiological tool for the early and accurate diagnosis of AD and MCI. However, certain methodological issues need still to be addressed before ERPs enter the arena of clinical practice.

What language abilities in Mild Cognitive Impairment indicate for cognitive abilities in aging?

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Abstract

Objective: Mild Cognitive Impairment (MCI) seems to be the interval between normal aging and mild Alzheimer's disease. This study aims to investigate if despite the cognitive decline there are significant deficits in language abilities between amnestic MCI(aMCI) and non demented elderly participants as helpful indexes for the diagnosis of the disease. **Subject and Methods**: Ninety participants, 45 non demented elderly and 45 aMCI recruited randomly as outpatients of the B' Internal Medicine of the Hippokrateion hospital of Thessaloniki, in Greece. They were matched in age and education and they were administered physiological, neuropsychological, and neuroimaging exam and the Boston Diagnostic Aphasia Examination (BDAE) for the language assessment. **Results**: From the 28 subtests of the BDAE, we found statistically significant differences between groups only in verbal fluency (categorical) and comprehension ability subtests, which both of them presuppose processing and storage requirements and are strongly correlated with working memory function. **Conclusion**: Our findings reinforce the hypothesis that aMCI people are not generally able to handle both processing and storage requirements simultaneously and devote their resources to one of these functions at the detriment of the other.

The present and future of functional (SPECT) imaging in dementias

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Abstract

Dementias present with high morbidity and mortality in ages over 65. Alzheimer's disease (AD) is the most frequent, accounting up to 70% of all. Diagnosis of AD, based on clinical criteria, is difficult in many cases. Anatomical imaging modalities can add in differential diagnosis, especially in cases of vascular component of dementia. Functional SPECT imaging using a lipophilic compound is a valuable tool in the diagnosis of AD and other types of dementia. In cases of AD, temporo-parietal hypoperfusion, plus posterior cingulated and precuneous involvement are present. However, in early cases, medial temporal hypoperfusion is evaluated as a premature sign of AD. The same finding can be a marker of AD invasion in cases of mild cognitive impairment. The second cause of dementia is Lewy-body encephalopathy (LBE), in which occipital hypoperfusion is a differential criterion from AD. In the above mentioned cases, SPECT imaging of the nigro-striatal system with Ioflupane, is of great value, showing intact integrity in AD and reduced in LBE. Vascular dementia is diagnosed in combination with SPECT imaging in combination with anatomical imaging modalities. The challenge of SPECT imaging is the early diagnosis of dementias, especially of AD, the clinical impact on treatment and the hereditary factors in the appearance of AD.

Techniques and quantitative measurements in brain imaging with SPECT and PET

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Abstract

Nuclear Medicine plays an important role in the diagnosis of serious neurological diseases like Parkinson's, and more recently, Alzheimer's disease. Nuclear Medicine using Single Photon Emission Computed Tomography (SPECT) with γ-camera and the appropriate radiopharmaceutical provides a means for the differential diagnosis between Parkinson's disease and Essential Tremor or Parkinson's Plus syndromes. Recently, specialized radiopharmaceuticals gained approval to be used with Positron Emission Tomography (PET) in imaging the deposition of β-amyloid in brain areas, a situation that has been associated with Alzheimer's disease. While visual assessment of SPECT or PET images is the basic method of diagnosis, since the first days of neuroimaging quantitative methods has been proposed towards the objectification of the diagnosis. International associations consider reporting quantitative data coming from appropriate measurements done after the scintigraphic evaluation of neurologic diseases, as being mandatory, in addition of course, to visual assessment. Applying quantification can enhance the method's sensitivity, can be used for patient's follow-up and establish a common ground between centers in multi-center trials. Assessment of longitudinal change requires, also, some form of quantification. In the early days, true quantification used complex models of compartmental analysis requiring cruel procedures like multiple arterial blood sampling from the patient. Since that kind of methods couldn't be part of an "every day" clinical protocol, semi-quantification methods based on computers and appropriate software were developed. As far as Parkinson's disease is concerned, semi-quantification methods are being used for the determination of the specific binding of the radiopharmaceutical in the Structures of Interest (Striatum, Caudatum, Putamen) in relation to a brain area that does not show specific uptake e.g. the occipital cortex. In Alzheimer's disease, semi-quantification methods are being used for the determination of the Standardized Uptake Value Ratios (SUVRs) between Areas of Interest and again a Reference Area like the pons or the cerebellum. In quantification, the trend is towards advanced and automated software packages for saving time, easiness of use, objectivity and reproducibility.

A review on the diagnostic utility of EEG for the diagnosis of dementia related disorders and Mild Cognitive Impairment

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Abstract

The electroencephalogram (EEG), occupies an important position as a diagnostic and research tool for dementia-related disorders. Despite the important developments of other powerful techniques, the research interest on EEG, has grown over the last decades, because of its main characteristics: low-cost, simple to use, non-invasive, brain activity can be monitored in the freely moving subject, high time resolution. The characteristics of EEG signals, depend on the amount of correlation between the active neurons, hence neural changes associated with dementia, can be detected with EEG, for example through Event Related Potentials and quantitative electroencephalography. EEG could be used not only as a clinical biomarker for diagnosis and classification, but also as a tool for predicting the stages of dementia.In this work, we review, up to recent developments, the role of EEG as a neurophysiological biomarker in the detection of dementia-related disorders, highlighting the four most frequent types of dementia, Alzheimer's Disease, Vascular Dementia, Lewy Bodies and Parkinson's Disease. Additionally, we report the EEG features in Mild Cognitive Impairment.

Correlating cognitive status with electrophysiological brain networks: methodological aspects and preliminary results in healthy volunteers

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Abstract

Background: High-density EEG (hd-EEG) is being increasingly employed as a means of investigating the integrity of brain networks in health and disease. The optimal usage of this technique requires the elucidation of important methodological aspects and the application of the method in healthy subjects prior to the investigation of patient cohorts. Subjects and Methods: Ten neurologically normal subjects (aged 19-47 years of age) entered the study after giving informed consent for the procedures which were approved by an institutional review board. hd-EEG was performed in electrically shielded conditions using a 64-channel hd-EEG device (TMS-compatible eXimia, Nexstim Oy,Finland). During acquisition, the reference channel was attached to the right mastoid and the ground electrode was placed on the right zygomatic bone at a distance of approximately 4 cm from each other. The EEG signals were band-pass filtered from 0.1 to 500 Hz and sampled with a 1450 Hz sampling frequency and 16-bit precision. For data analysis, we selected artifact-free channels and preprocessed the data by applying a band-pass filter (low pass frequency 0.01 Hz and high pass frequency 70 Hz, filter order 60) and downsampling to 200 Hz. The EEG data were then re-referenced to infinity as well as to common average. Brain networks were constructed in artifact free epochs during resting state using linear and non-linear measures of brain connectivity. Conclusion: High-density EEG can be used to construct and describe brain networks quantitatively. The importance of certain methodological aspects in this procedure is highlighted.

CSF biomarkers in every day practice

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Abstract

Although dementia has early warning signs and symptoms, a “possible” or “probable” diagnosis can be a difficult, lengthy and intensive process. An early diagnosis is even more difficult, since early signs of dementia are very subtle and vague, and may not be immediately obvious. Early and accurate diagnosis is however important for many reasons. Several modalities show promise as diagnostic tools for Alzheimer’s disease (AD) and other dementias. These include: magnetic resonance imaging (MRI) measurements of atrophy, positron emission tomography (PET) imaging of glucose metabolism and of Aβ deposits and cerebrospinal fluid (CSF) biomarkers namely tau, p-tau and Aβ42 for tauopathy and amyloidopathy. A strongly positive family history, leading to mutation screening, can additionally provide a specific diagnosis for a small number of hereditary dementias. New diagnostic criteria proposed for AD [Dubois et al. Lancet Neurology 2007; 6:734-746 and National Institute of Aging & Alzheimer Association (http://www.alz.org/research/diagnostic_criteria/)], incorporate biomarkers as supporting evidence for the diagnosis. In the present round table we present clinical cases in which CSF biomarkers were helpful in clinical and differential diagnosis of various dementia syndromes.

“Theatre of the Oppressed” applied to Alzheimer’s caregivers

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Abstract

Caregiver’s burden is an all-encompassing term used to describe the physical, emotional and financial toll of providing care. According to recent data, supporting caregivers is the number one guideline towards facing dementia. In a support group, caregivers learn from the experiences of others who have faced the same challenges. We propose a new idea about caregivers support groups, which combines both education, support and public awareness for dementia. The Theatre of the Oppressed is based on the methodology created by Augusto Boal. In the first part of the therapeutical intervention the participants of the group discuss their feelings and experiences in relation with the care they provide. On the same time they create a script in which the “protagonist” is the care giver, who is confronting stressful events from their everyday caring experience. In the second part the participants present a performance based on their script. The performance is being presented on the audience of the carrent Conference for dementia. The actors begin with a dramatic situation from their everyday life with a patient and try to find solutions. For example they could start by acting how they deal with everyday behavioral problems the patient may have, or misunderstandings with secondary caregivers, or lack of understanding from doctors, etc. Audience members are urged to intervene by stopping the action, coming on stage to replace actors, and enacting their own ideas. At the end audience and participants have the change to disgust the feeling of ”katharsis” ,the protagonist may have after the end of the performance, and propably how themselves could reach” katharsis” in their everyday life. The whole process is a change for education, support and awareness for both participant and audience in an experiential way.

Sideritis (mountain tea) and Salvia (sage) species: natural sources as potential drugs in the treatment of Alzheimer's disease

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Abstract

Alzheimer’s disease (AD) is a neurodegenerative disease that primarily affects the elderly population over 65 years of age, is estimated to account for about 70% of the dementia cases, and now affects approximately 24 million people worldwide. Current AD treatment is symptomatic and is mainly, but not exclusively, focused on the inhibition of cholinesterases (ChEs). Medicinal plants have been evaluated for the treatment of AD, particularly those belonging to the Lamiaceae family. Members of the Lamiaceae family and their phytochemicals have been studied for pharmacological and some clinical effects relevant to dementia. One of the most well-known Lamiaceae family plants is the genus Salvia, which has wide distribution, with nearly 1000 species. The genus Salvia is a huge and important source, rich in terpenoids and flavonoids and other phenolics with antioxidant, anti-tuberculous, anti-inflammatory, neuroprotective, and anticholinesterase properties. Species of this genus, such as S. officinalis, possess significant pharmacological activities and have been used against memory loss in Europe. S. officinalis is used as an herbal medicine for neuronal dysfunction. It has many antioxidant compounds with high activity, particularly carnosic acid (diterpene) and rosmarinic acid (stilbene). These compounds are thought to protect the brain from oxidative damage. Plants of the genus Sideritis (family Lamiaceae) are widely used in folk medicine in the Mediterranean region. The decoction and/or the infusion of aerial parts is traditionally used as an antimicrobial, anti-inflammatory, antiulcerative, anticonvulsant, antispasmodic, and carminative agent. So far, a wide variety of biological activities of the Sideritis species have been reported: anti-inflammatory, anti-ulcer, analgesic, antimicrobial and antifungal, antifeedant, anticataract, immunomodulating, macrophage NOS-2-expression inhibiting, hypoglycaemic, aldose reductase-inhibiting activity, antiproliferative and anticholinesterase have been reported. The common Greek name of these plants is “mountain tea” and their activity is mainly due to their flavonoid, phenylpropanoid glycosides and terpenoid content.

Effects of Ginko biloba extracts on memory. Basic studies and clinical applications

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Abstract

Memory-related disorders are a common public health issue. Memory impairment is frequent in degenerative diseases (such as Alzheimer's disease, Parkinson disease), cerebral injuries and schizophrenia. Ginko biloba (G. biloba) is one of the oldest living trees species on the planet. G. biloba extracts are widely used in folk medicine for various purposes. Several lines of evidence suggest that GB is implicated in cognition. In this context, it has been reported that G. biloba extracts might reduce or even prevent the cognitive decline associated with aging. Here we critically review advances in research of this emerging molecular target for the treatment of memory disorders, discuss its potential advantages over currently used cognitive enhancers as well remaining challenges.

Recent developments in ICT sector for people with dementia and informal caregivers in Greece

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Abstract

Recent years have seen a rapid growth in the research and development of new technologies in order to improve services and enhance the independence and quality of life of people with dementia and their caregivers. This abstract reviews some of the trends in research and development in the area and assesses the implications for the provision of care and services for people with dementia and their caregivers in Greece. The review indicates that the use of information and communication technologies (ICTs) could play a significant role in the delivery and support of community care services. Information and communication technology (ICT) may offer new ways of reducing caregiver burden through information provision and social contact. Athens Alzheimer's Association runs 4 ICTs programs for people with dementia and their caregivers. More specific, for people with dementia we implement the following programs: **1. Long Lasting Memories (LLM)** is an EU project aiming at an integrated ICT platform which combines cognitive exercises with physical activity in the framework of an advanced ambient assisted living environment. LLM delivers an effective countermeasure against age-related cognitive decline. **2. SOCIABLE: Touch Screen Computerized Cognitive Training Program** is an innovative EU project where cognitive training program is carried out on a touch-screen computer. It aims to exercise and improve the cognitive abilities by compromising a variety of creative games-exercises targeting memory, perception, attention, language, visuospatial abilities and orientation. Additionally, the ICTs programs currently offered by Alzheimer's Associations in Greece to caregivers are the following: **1. INNOVAGE project.** The INNOVAGE project is dedicated to developing and cataloguing, social innovations for older people. Italian National Institute of Health and Science on Aging and Eurocarers Association are the partners responsible for developing and implementing a multilingual web platform for informal carers in 27 EU Member States. **2.SET CARE.** The overall aim of the project is to improve the skills of care workers in Greece and Bulgaria by adapting an innovative Italian e-learning tool called ASPASIA in the frame of a Lifelong learning Programme: Leonardo DaVinci and focus on themes such as: healthcare skills, assistance skills, rights and duties of the care worker, national health and service systems e.t.c. **3. Supportive sessions for caregivers via Skype.** Alzheimer Hellas Organization launches a program with the use of Skype video conferencing in order to connect health care professionals with patients' caregivers for counseling and psycho education.

Alzheimer's Disease and dietary supplementation

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Abstract

Although it is well established that AD constitutes a multifactorial, chronic, degenerative disease, a simple search on the mass media will soon reveal a profusion of information and proposals of treatments with certain "magic pills" alias "elixirs" that promise miraculous results on the stopping of progression or even inversion of the disease and representing a flourishing industry. Only a small fraction of these claims, though, are supported by sound and adequate scientific research. An area where scientific proof is sound is that of caloric and/or protein supplementation of Alzheimer's patients in the process of losing or at high risk of losing body weight as it is known that weight loss is accompanied with worsening of the cognitive status. Pharmaceutical industry research is interested, among others, in the discovery and development of medical foods that is of "foods formulated for enteral taken under physician supervision, and intended to meet the distinctive nutritional requirements identified for a disease or condition". The list of substances used so far include n-3 polyunsaturated fatty acids, Gingko biloba leaf extracts, antioxidants (like lycopene, quercetin, resveratrol, curcumin, etc.), antioxidant vitamins (like β-carotene, C and E), vitamin D, certain vitamins of the B complex, selenium, aloe extracts, tauroursodeoxycholic acid(TUDCA), S-adenosyl methionine (SAM). The kind and level of available supporting evidence for each one of these substances is different and varies from experimental in vitro studies and animal models to epidemiological studies. Few are the available observational and intervention studies and even lesser the randomized control trials (RCTs) or the meta-analyses. A comparative table is briefly presented using a critical approach of the available publications. At this moment the most promising molecules seem to include Vitamin D and n-3 polyunsaturated fatty acids and possibly Vitamin E. Evidence is also presented concerning certain commercially available combinations., C and E),ycopene, rsveratrol,e omega-3 polyunsaturated fatty acids, Gingko Biloba leaf extracts,

Olive oil: a new source of agents against Alzheimer's disease

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Abstract

Olive oil is one of the most important ingredients of the Mediterranean diet. Recent studies have shown that it is a rich source of unique chemical agents like oleocanthal, oleacein, oleuropein aglycone and ligstroside aglycone. All these phenolic compounds possess interesting biological activities including anti-inflammatory, cardioprotective and neuroprotective properties. Their health protecting activity has been recently recognized by the European Union that has adopted an official health claim for olive oil.

The presentation will focus on the recent promising studies about the activity of oleocanthal and oleuropein aglycon on the prevention of Alzheimer's disease in in vitro and in vivo models. In addition we will present the results of a 5-year screening concerning the levels of the two active ingredients in more than 2000 olive oil samples as well as a summary of the factors that influence the levels of these compounds in olive oil (e.g. variety, harvest period etc).

Recent findings in Alzheimer's disease and nutrition focusing on epigenetics

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Abstract

Purpose of review: Alzheimer's disease is a chronic neurodegenerative disease with no effective cure so far. Due to its growing prevalence, Alzheimer's disease tends to become, apart from a health problem, also a socio-economic problem. It is therefore crucial that new ways are found in order to treat the most unclear and yet most frequent kind of dementia. The current review focuses on the epigenetic mechanisms of Alzheimer's disease and how nutrition can influence the course of this disease through regulating genes expression according to the latest scientific findings. **Recent findings:** Epigenetics is becoming a very attractive subject for the researchers as it can shed light on unknown aspects of complex diseases like Alzheimer's dementia. DNA methylation, histone modifications and microRNAs (miRNAs) are the principal epigenetic mechanisms involved in Alzheimer's disease pathophysiology. Nutrition is an environmental factor which is related to Alzheimer's disease through epigenetic pathways. The research results might seem ambiguous about the role of nutrition, but there is strengthening evidence that proper nutrition can not only change epigenetic biomarkers levels but can also prevent the development of late-onset Alzheimer's disease (LOAD) and cognition attenuation. **Summary**: Nutrition is growing to become a useful preventive and even therapeutic alternative against Alzheimer's disease especially if combined with other anti-dementia treatments, such as acetylcholinesterase inhibitors, brain exercise, physical training etc. Epigenetic biomarkers can be a very helpful tool for the researchers to find the exact nutrients needed to create specific remedies and maybe the same biomarkers can be used even in patients screening in the future.

Organization of mental health and psycho geriatric services

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Abstract

Objective: Public awareness about the need for care of patients over 65 years. To emphasise *the need* the of organized plan of action, education and awareness of medical and paramedical staff, as well as other people working and care of the elderly. In our country there are now 200,000 patients with dementia and this number is constantly growing. Short Historical Review of psychiatric reform in Greece. The third phase of PSYCHARGOS program covers the period 2010-2020. A well organized working group needed to prepare a Draft Revised Programme "Psychargos 2011-2020". At the G8 summit in London (December 2013) co-signed a commitment to expanding the efforts to combat dementia. The November 2013 established "Working Group to develop a National Action Plan for Dementia- Disease Alzheimer» and the agree on an international approach for future dementia research. **Material and Method:** researches of Greek and foreign literature. **Conclusion:** There is a lack of Psychogeriatric structures and services in the region and in major urban centers. With an ageing population, dementia is soon to become the biggest burden on healthcare systems around the world. Further awareness and develop these structures needed. It is also important lifelong education of mental health professionals.

Brain imaging biomarkers for early diagnosis of Alzheimer's disease: MRI, functional MRI and functional connectivity MRI

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Abstract

The diagnosis of AD relies on both specific memory deficits and in biomarkers. Pathologic abnormalities associated with AD develop in the brain 1 to 2 decades prior to development of first memory symptoms. If we could detect these abnormalities early in the course of the disease, we could probably take special strategies to suspend the evolution. Magnetic resonance imaging (MRI) of the brain is very useful for establishing an early diagnosis of AD, as well as monitoring disease progression. In this context, some MRI techniques could help to evaluate patients with dementia. Conventional MRI excludes other neurodegenerative diseases and detects better disease state and progression. Structural volumetric MRI metrics have much more power to detect changes than clinical measures. Moreover, they improve diagnostic efficacy and contribute to differential diagnosis of AD. Nonconventional MRI approaches are providing a complete picture of AD pathology in vivo: they detect and quantify the metabolite and microstructural abnormalities associated with neurodegeneration in AD. Proton magnetic resonance spectroscopic (^{1}HMRS) imaging and diffusion tensor (DT) MRI are sensitive to early changes and have the potential to identify patients early in the course of AD. In addition, the use of functional MRI (fMRI) has provided new insights into the role of cortical adaptive changes in AD and may offer additional imaging markers for detecting early abnormalities and monitoring the disease progression under specific treatments. Having the advantage of no need for cooperation of the examined subject, functional connectivity (fc)-MRI is a good method to detect changes in AD brains. Monitoring alterations in functional brain activity related to visual processing deficits in AD has strong potential as an early diagnostic biomarker.

SPECT and PET approaches for early diagnosing dementia and MCI

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Abstract

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are imaging modalities which help the clinician to investigate the functional and neurochemical changes of the brain, in patients with dementia and in those at risk of subsequent cognitive decline. PET ligands are developed for demonstration of amyloid plaques and thus early diagnosing of AD. Emission tomography, with highly specific new ligands will have more increasing application in both, dementia research and patient management in the future. AD with several pathophysiological characteristic features (amyloid plaques, neurofibrillary tangles, several neurotransmitter deficits) is a common cause of dementia in elderly and still its early diagnosis and treatment remain challengeable. The application of emission tomography in dementia will be discussed here and we will be engaged to the contest that may SPECT and PET predict the future for Mild Cognitive Impairment (MCI)? And also since there is still no treatment for Alzheimer's disease what is the role of PET and SPECT in diagnosing of the disease? Are these studies cost-effective methods?

Prevalence of dementia in the oldest old

Ugo Lucca

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Abstract

Cognitive functioning declines with age and most individuals suffering from dementia are over-eighties. However, clinical studies systematically investigate patients with dementia who are younger than those found in the general population. Research in the oldest-old in fact is made difficult by the frequent presence of poor health, sensory impairments, frailty and fatigue, as well as by the problematic assessment of cognitive, occupational and social functioning. Conducting epidemiological studies in the oldest-old is thus a major challenge and the number of over-eighties included in surveys on dementia is usually small. This over-representation of young old individuals and under-representation of old old results in an age gap that may be an important source of bias and raises a problem of generalisability of the results. In the near future this age gap will become even wider since the over-eighties are the fastest growing segment of the elderly population. Based on the small numbers of oldest-old usually investigated, rates of the occurrence of dementia in this age segment fluctuate widely precluding any relevant conclusions. Accurate estimates of dementia prevalence are critical for a better understanding of the relation of aging with cognitive decline and dementia, and for the planning of future social and medical care for this ever increasing population. Elderly persons included in studies on dementia need to be representative of the population at risk if successful strategies to delay cognitive decline and thus reduce the burden of dementia on the individual and society are to be developed. To try to overcome these difficulties, since 2002 we have been conducting a prospective population-based study (*Monzino 80-plus Study*) specifically designed to investigate dementia and cognitive decline in a very large and representative population of oldest-old including a considerable number of individuals also in the extreme age groups.

Alzheimer's disease and subcortical vascular disease – from baseline to six-year follow-up; report from the Gothenburg MCI study

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Abstract

To improve the design of trials in Alzheimer's disease (AD), there is a need of paying attention to the interplay between AD and subcortical vascular disease, the latter representing a disease entity that may cause or contribute to cognitive impairment. Of the 664 patients enrolled in the Gothenburg MCI study between 2000 and 2013, 195 where diagnosed with subjective cognitive impairment, 274 with mild cognitive impairment (MCI), and 195 with dementia at baseline. Eighty-one of the dementia patients had AD, 27 subcortical vascular dementia (SVD), 41 mixed type dementia (=AD+SVD=MixD), and 46 other etiologies. After 6 years 69 of the baseline patients (24%) had converted to dementia [29 (42%) to AD, 15 (22%) to MixD, 16 (23%) to SVD]. The study, which is ongoing, has shown that it is possible to identify not only AD but also incipient and manifest MixD/SVD in a memory clinic setting and that there are neuropsychological and neurochemical differences between the disorders. These conditions should be taken into account in clinical trials.

Examination of the factors affecting subjective well-being in elders

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Abstract

Little is known about the variables that predict perceived well-being in elders. Based on the concepts of Positive Psychology, this study aimed to examine the effect of a number of factors upon the psychological well-being of elders. The study is still in progress and these are preliminary results. A sample of 72 elders (62.5% males) of mean age 73.4 (SD=9.1) were recruited from the day-care center, the domiciliary care, and the center for the open care of Gortyna's Municipality in Heraklion, Crete. They were married (63.9%), had one child (51.4%), and primary school education (70.8%). They were administered the Family Members' Interrelating Questionnaire (FMIQ), the Significant Others Scale (SOS), the Psychological Well-Being scale, the Satisfaction with Life Scale (SWLS), the Brief Symptom Inventory (BSI-18), and the Resilience Scale-15 (RS15). A multiple linear regression analysis (stepwise method) was performed to investigate the impact of a set of predictors [i.e., age, marital status, health problems, positive/negative relationships with child(ren), social support from friends/family, satisfaction with life, anxiety, depression, somatization, and resilience] upon the subjective well-being of elders. The model was statistically significant ($F_{(4)}$=36.020, p<.001) and predicted 70.4% of the variance in well-being. As anticipated, depression (β = -.231) and negative relationships with a child (β = -.222) were associated with lower well-being, whereas resilience (β= .398) and satisfaction with life (β= .252) were associated with higher well-being. The findings suggest that psychiatric disorder (e.g., depression) rather than physical frailty and a negative relationship with a child rather than social support from family or friends in general, have detrimental effects in elders' well-being. Geriatric practitioners should assess these factors regularly when working with elders and aim at buffering them from the negative effects of these risk factors, while at the same time, enhancing their resilience and satisfaction with life.

Mediterranean diet and dementia: the effect of dairy consumption and red meat

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Abstract

As the life expectancy tends to increase, various forms of dementia incidence rates are increasing as well constituting dementia as a major public health problem. Dementia is considered a multifactorial disease influenced by different elements modifiable and non-modifiable.To study the relationship of nutrition and dementia in recent decades, the scientific community has concluded, through plenty clinical and epidemiological studies, the important role of the Mediterranean diet.The Mediterranean diet is characterized by high intake of vegetables, legumes, fruits and cereals, higher oil intake compared with the low intake of saturated - trans fat, adequate intake of fish, low to moderate intake of dairy products, low intake of meat and moderate intake of ethanol, mainly in the wine form during meals. Greater acceptance of the model of MD appeared to be associated with lower risk of cognitive deterioration and AD as it is considered its protective role against brain neurons oxidative stress. Reference is made to the reduction of linoleic acid intake of margarine, butter and dairy products. Researches support relationship between increased calcium intake and brain function. Worth noting that several studies reported low in fat, dairy products, combined with a balanced diet, provide several benefits for the human. Important reporting the correlation of animal fat and memory impairment. Surveys show the relationship of iron intake in individuals who consumed red meat and butter often, lard or fried foods opposed to those who mainly fed with vegetables, poultry and fruits. In general, studies show that reducing the BMI several vascular factors are affected and the risk for dementia is modified. Highest compliance to MD is associated with lower risk for AD, lower mortality and longer survival.

Caregivers of elders and dementia patients residing in care units: A comparative study examining the factors affecting their well-being

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Abstract

This study aimed to examine the factors that affect the quality of life of the caregivers of elders and those of dementia patients residing in care units. The study is still in progress and these are preliminary results. The sample was sixty five caregivers in 6 care units for elders in Athens and Crete. Of them, 53 were caregivers of elders and 12 caregivers of dementia patients. Fifty seven were women (87.7%), with mean age 34.1 years (SD=8.5), with higher degree education (43.1%) and 6.7 mean number of caregiving. The caregivers had good relationships with their child(ren), high support from friends and family, high subjective well-being and resilience, and low somatization, anxiety, and depression scores. There was no statistical significant differences in terms of their place of residence (Athens - Crete) or the years of caregiving (>9 - <10). However, dementia caregivers had statistical significant higher levels of anxiety (8.33) and depression (7.33) in comparison with those of the caregivers of the elders (3.78 and 3.40, respectively. $t_{(59)}$= -2.696, p=.009 και $t_{(56)}$= -2.394, p=.020). A multiple linear regression analysis (stepwise method) was performed to investigate the impact of a set of predictors [i.e., marital status, years of caregiving, positive/negative relationships with child(ren), social support from friends/family, satisfaction with life, anxiety, depression, somatization, and resilience] upon the subjective well-being of the caregivers. A similar analysis for the dementia caregivers was not possible due to the small sample size. The model was statistically significant ($F_{(2)}$= 23.737, p<.001) and predicted 60.3% of the variance in well-being. Resilience (β= 3,811) and satisfaction with life (β = .648) were associated with higher well-being. The comparison with other groups of caregivers (e.g., caregivers of dementia patients, or psychiatric patients) of adequate sample size, is necessary to confirm the study results.

Financial capacity and dementia: To be or not to be an APOE e4 carrier?

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Abstract

According to the literature the ε4 allele of the apolipoprotein E (APOE ε4) gene is not only considered to be a risk factor for developing Alzheimer's Disease, but also it has a strong negative influence on cognition of healthy elders and patients alike. This study aims to examine if dementia patients who are carriers of the APOE ε4 gene have a different neuropsychological profile from the patients who are not APOE ε4 gene carriers concerning their financial capacity. Seventy-nine patients with a diagnosis of dementia (Mage=74.82, SDage=8.32, Meducation=7.95, SDeducation=4.21) at the time of the neuropsychological examination underwent a blood test. Results revealed that there were no statistically significant differences for the Mini Mental State Examination, the Functional Rating Scale for Symptoms of Dementia, the Geriatric Depression Scale and the Legal Capacity for Property Law Transactions Assessment Scale between the groups of patients who were APOE ε4 carriers and those who were not. Statistically significant differences were found only when the participants were grouped according to their educational level. In conclusion, financial capacity seems not to be affected by the presence of the APOE ε4 gene, but other factors seem to play a crucial role.

Amyloid encephalopathy and financial capacity: A case study

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Abstract
This study aims to examine the financial capacity of a previously functional patient suffering from Amyloid Encephalopathy. A 75-year-old patient with 3 years of education, and at the time of the examination a retired driver, underwent a neuropsychological assessment (MMSE = 9, GDS = 1, FRSSD = 26), and examined with a new scale, the Legal Capacity for Property Law Transactions Assessment Scale (LCPLTAS). Results revealed that although the patient was claimed to be able to handle his financial affairs until recently, at the time of the neuropsychological examination the patient scored below normal on all 7 domains of the LCPLTAS: 1) basic monetary skills (0/14), 2) cash transactions (0/8), 3) bank statement management (0/8), 4) bill payment (0/8), 5) financial conceptual knowledge (3/32), 6) financial decision making (4/114), and 7) knowledge of personal assets (2/28). These results give us a different neuropsychological profile when compared with a 77-year-old patient with severe Alzheimer's disease (retired merchant, 4.5 years of education, MMSE = 9, GDS = 2, FRSSD = 15), who scored differently on all 7 domains of the LCPLTAS: 1) basic monetary skills (0/14), 2) cash transactions (0/8), 3) bank statement management (0/8), 4) bill payment (0/8), 5) financial conceptual knowledge (0/32), 6) financial decision making (0/114), and 7) knowledge of personal assets (0/28). In conclusion, this case study reveals that Amyloid Encephalopathy has a strong influence on financial capacity. Further studies are suggested on the clarification of the financial profile for this group of patients from patients with Alzheimer's disease.

The effect of dancing in people with Parkinsonism

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Abstract
Parkinson's Disease (PD) is a neurodegenerative disease associated with symptoms such as tremor, rigidity, bradykinesia, freezing during gait, motor control deficits and instability. These physical symptoms can cause a lot of psychological problems including depression, feeling of loneliness, and low self-esteem. It is a common belief that PD is associated with a progressive decline of mental and physical abilities. The critical role of exercise, maintaining physical and mental health of elderly people is well-acknowledged and so there is a need for guidelines permitting an independent and healthy life into old age. Dance has shown to be a beneficial activity for this population. Upon reviewing recent dance for PD studies it is clear that there are developing trends with respect to overall approach. Dance as therapeutic intervention, combines emotions, social interaction, sensory stimulation, motor coordination and music, creating enriched environmental conditions for people. There is a lot of studies which showed the positive impact of dance in the elderly suffering from neurodegenerative diseases. Also, many studies showed that contemporary dance works as training for change, inducing plasticity in flexible attention. With growing support for exercise to improve not only motor symptoms, but also cognitive impairment in PD, health care providers and policy makers should recommend exercise as part of routine management and neurorehabilitation for this disorder. In this review we show the effects of the dance therapy, as it has been proved from many studies and meta-analysis not only in physical health but also to psychological aspect of patients with Parkinsonism and discuss ideas for future research.

Overview of the Dem@Care project

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Abstract

The Dem@Care project aspires to provide meaningful support for individuals with dementia, allowing them to remain independent for a longer period of time, as well as assist their carers to better understand their condition and its progression. This is achieved through multisensory monitoring of the person with dementia, followed by intelligent fusion to provide high-level outcomes and personalized support. The goals of the monitoring are dictated by clinical experts, for the meaningful assessment of the person's cognitive status and their ability to live independently. At the same time, personalized feedback is provided to the person with dementia and more detailed feedback is provided to their carer, providing them with a comprehensive view of the health status and progress of the affected person. The person with dementia can thus have an increased sense of safety and security, without significantly modifying their lifestyle. Clinicians can integrate the Dem@Care solution in their current workflow, as it will provide them with an accurate picture of the person's condition and its progression, allowing for more effective personalized care.

Presentation of the Dem@Care lab and home pilot setup and testing and outcomes in Thessaloniki

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Abstract

The integrated Dem@Care system was tested in real world pilots to examine and verify its effectiveness. Participants were recruited from GAADRD, aged over 65, of both genders, and with conditions ranging from mild cognitive impairment to dementia. All participants and their informal carers were briefed on the monitoring and its goals, and signed informed consent forms, thus addressing privacy and ethical concerns. Multiple sensors were deployed in a home-like environment that was set up in the lab, including motion, audio, visual, electricity sensors, to monitor the person's performance while performing semi-supervised daily activities dictated by clinical experts. The multi-sensor results were fused intelligently, to obtain a high level picture of the person's condition and relevant outcomes were sent as feedback. Simpler feedback is always provided to the person with dementia, while detailed feedback is sent to their carers. Similarly, the Dem@Care system was tested in a real-world home environment, for daily life monitoring, to create lifestyle and behavioural profiles of the person being monitored. Monitoring of the person in their home is expected to provide useful insights on their condition and its progression over time, for improved personalized care and increased independence.

The use of ICT for the assessment of pre-demented and demented patients within the Dem@care project

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Abstract

Introduction: Currently, the gold-standard for the assessment of cognitive and functional abilities involves questionnaires and clinical rating scales. However, these are often limited in their ability to provide objective and sensitive information. In contrast, information and communication technologies (ICT) may overcome these limitations by capturing more fully the disturbances associated with Alzheimer disease (AD). We investigated the use of different sensors, such as a video monitoring system or audio analyses for the assessment of dementia and pre-demented patients. Methods: Three groups of participants (healthy control, Mild Cognitive Impairment and Alzheimer's disease) had to carry out a standardized scenario consisting of directed tasks (single, dual task and vocal tasks) and activities of daily living such as preparing pillbox while being recorded. The performance quality of each participant was manually annotated and assessed based on the amount of successfully carried out tasks. Recorded data was processed by a platform of signal analysis in order to extract parameters detecting activities undertaken by the participant. We developed a classifier based on the extracted features for diagnostic prediction and further autonomy performance prediction. Results: Overall, activities and task performances were detected automatically with high accuracy rates (up to 80%). Further detailed results from the audio, gait and video analyses will be presented at the conference. Conclusions: The results suggest that it is possible to assess dementia and pre-demented patients autonomy with the help of ICT and in particular, an automatic video monitoring, audio analyses and accelerometers and that the use of such technologies could provide clinicians with diagnostic relevant information and improve assessment in real time decreasing observer biases.

Dementia ambient care: Home-based monitoring and enablement of people with dementia

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Abstract

Background: The prevalence of dementia is expected to increase as our population ages. Enabling people with dementia to remain living well at home for longer increases their quality of life, as they remain integrated in their families and communities. However, cost-effective home-based solutions are needed to support the autonomy and independence of the person with dementia at home, thereby reducing caregiver burden. Ambient assistive technologies present opportunities to support these goals while providing clinicians with objective assessments of the individual with dementia over time. Methods: Dem@Care is an EU-FP7-funded initiative using ambient and wearable sensors to monitor and support five frequently problematic areas for a person with dementia: physical activity, sleep, activities of daily living, social interaction, and mood. A clinical assessment identifies a person's unique needs in each domain, and an individualised sensor 'toolbox' is jointly agreed to support these needs. Aggregated sensor data identifies behavioural changes over time that could signify improvement, stasis, or deterioration of function. Results: We report findings from two Dem@Care home pilot studies from the perspective of the clinician, the caregiver, and the person with dementia. We present results from user-centred design of the Dem@Care system; the monitoring of physical activity, sleep, activities of daily living, and quality of life; the acceptability and usability of the sensors in the Dem@Care toolbox; and we explore Dem@Care's potential to support the delivery of cognitive and psycho-social interventions in the home. Conclusions: Dem@Care findings illustrate that multi-sensor monitoring and assessment systems have the ability to preserve autonomy and enable living well at home with dementia. The objective patterns of behaviour in and across functional domains not only assist the individual and their family, but also the clinician, who gains valuable insight into an individual's behavioural and cognitive changes over time.

Assessment and evaluation of interventions in BPSD with the help of a multiple sensor system

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Abstract

Introduction: Clinical assessment of BPSD in advanced stages of dementia is often based on staff member's observations and the use of the NPI-NH instrument. A challenge is the validity of the observations. Structured information from electronic sensors, measuring patterns of behavior as sleep, physical activity and stress/anxiety may contribute to overcome these problems by providing relevant accurate information on patterns of behavior. We have studied the impact and feasibility of using the information from sleep sensors, sensors of activity and stress/anxiety in the clinical assessments that are based on the NPI-NH instrument. Methods: The study is carried out in the context of specialist dementia care units in northern Sweden where the staff were trained to use the NPI-NH instrument in structured assessments of BPSD and evaluation of interventions. Residents from the two units served as an intervention group and were equipped with sensors for monitoring patterns of sleep, physical activity and anxiety. Participants residing in two similar units served as control. The structured assessments involved a process of NPI-NH assessment, analysis of the problem, an intervention, and evaluation of the results, which was carried out at the beginning, in the middle and at the end of a two month's cycle. Results: The results indicate that access to sensor information on patterns of sleep, physical activity and stress/anxiety can have an impact on the quality of the clinical assessment process in people with BPSD and the evaluation of care interventions. The understanding of patterns of behavior can improve and as a consequence the efficiency of care interventions. Further detailed results from a comparative analysis of the assessment process in the two groups of participants will be presented at the conference. Conclusions: The results suggest that the process of assessing BPSD, using proper interventions and evaluating them can be improved by adding structured sensor information on patterns of sleep, physical activity, and stress/anxiety.

Cognitive impairment in multiple sclerosis

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Abstract

Although it is difficult to determine the frequency of cognitive deficits, studies involving the use of neuropsychological tests have demonstrated that impairments in superior cognitive function may occur in 40-65% of MS patients. Such deficits, which will affect aspects of the patients' daily life, will occur in only 5-10% of the said patients. Cognitive functions which will be affected normally include attention skills short memory, information processing speed, executive functioning, verbal fluency as well as visual space perception. These deficits will occur at a greater frequency in patients who have been suffering for many years. However, we cannot exclude the possibility that deficits might also occur during the early stages of the disease. There is no established link between the cognitive deficits and the degree of disability. Thus, a patient with no physical disability maybe affected by a more severe cognitive impairment compared to a patient with high degree of disability. The decline in cognitive functions often affects the patients' personal as well as professional life, while depression, stress and fatigue deteriorate the specific condition significantly. Provision of adequate information to the patients, prompt symptom evaluation by a neuropsychologist and a speech/language therapist as well as attending courses about the cognitive rehabilitation contribute remarkably to addressing and ameliorating cognitive deficits.

The pathophysiology of cognitive dysfunction in multiple sclerosis

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Abstract

Cognitive dysfunction is a common manifestation of multiple sclerosis (MS) affecting 40 to 70% of cases, which until recently remained unrecognized. According to MS patients it is the disease manifestation with the gravest impact on their quality of life and the strongest predictor of MS patients leaving the workforce. The cognitive functions most commonly affected in MS patients are working memory, attention, executive function and speed of information processing. Typically, cognitive dysfunction is irreversible and can be present from the earliest stages of the disease, including clinically isolated syndrome (CIS). Cognitive dysfunction is more common and more severe in the progressive forms of the disease rather than in the relapsing-remitting or the CIS stage. Nevertheless, cognitive impairment in MS does not appear to correlate with the overall level of physical disability. To date, a number of histopathological and imaging studies have attempted to examine the pathophysiology of cognitive dysfunction in multiple sclerosis. Except for the typical focal white matter demyelinating lesions recent evidence indicates a role for the cortex and deep gray matter structures. In addition, neuronal and axonal loss and synaptic disconnection appear to constitute the basis of cognitive impairment at the cellular level. Here, we aim to present and discuss a number of studies that shed light to the pathogenetic mechanism that underlie cognitive impairment in multiple sclerosis.

Cerebral atrophy as disease progression marker in multiple sclerosis

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Abstract

The loss of cerebral volume associated with the gray and white matter atrophy has been reported in patients with MS. The role of reduction of gray matter in this pathology has become increased attention object and that's because a number of histopathological and magnetic imaging studies show that the cortical lesions are more common than assumed. The studies measuring the volume of gray matter agree to the same conclusion: patients with MS show atrophy of gray matter compared with healthy controls. Cerebral atrophy starts early in the first demyelinating event slowly and gradually progresses in relapsing remitting. The assessment of disability in multiple sclerosis is generally estimated using the EDSS (expanded disability status scale). Recently is being used an overall functional score (MSFC) which takes into account the addition of mobility and cognitive parameter (attention, working memory and processing speed through the PASAT test).The cognitive symptoms in multiple sclerosis vary from deficits in processing speed and episodic memory to unusual occurrences with aphasia. The most common disorder relates to information processing speed. This reduced speed affects the appearance of disorders in other fields of knowledge, including working memory, executive function and revocation. Cerebral atrophy in early stages of relapsing-remitting multiple sclerosis has brain tissue loss rate at around 0.6 - 1.35% per year. Compared with a decrease of 0.1- 0.3% per year in the healthy population. Approximately 50% of patients with MS will develop cognitive disorders. Usually they are related to information processing speed, in recent memory, concentration, recall and executive function. Many clinical studies have shown the relationship between brain atrophy and cognitive impairment, such as studies of fingolimod TRANSFORMS and FREEDOMS. Now the rate of brain atrophy tends to establish itself as a reliable prognostic marker for disease progression.

Alzheimer disease co-morbidities

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Abstract

Alzheimer's disease is a chronic, progressive and neurodegenerative disease of the brain initially runs with disorders of higher cortical function, leading to dementia and a complete failure. In terms of clinical, neuropathological, biochemical and molecular level, Alzheimer's disease is heterogeneous and can take place accompanied by a number of disorders and disease entities. The burden of medical comorbidity is greater than matched individuals without Alzheimer disease. There is psychiatric and non-psychiatric comorbidity associated with Alzheimer disease. Among the psychiatric co-morbidities are: depression, delusions, hallucinations, agitation and aggression, which could be either part of the dementia or an undiagnosed condition that needs to be addressed and treated. On the other side physical comorbidities make important contributions to cognitive and functional decline and have important implications for healthcare providers. Such diseases could be: vascular disease, diabetes, ocular diseases, abnormal weight loss, sleep disorders, loss of bludder and bowel control and sexual dysfunctions. The comorbidity is a major determinant of independency loss and is associated with faster cognitive deteriorioration. In any case it is important to keep in mind that the successful management of patient with Alzheimer is not only the treatment of memory loss but all the spectrum of symptoms of the disease.

Amyloid beta-oligomers: a target for Alzheimer therapy?

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Abstract

Immunotherapies targeting both soluble and insoluble aggregates have succeeded in lowering deposits of beta amyloid in brain but not to produce significant clinical results. Many candidates of soluble oligomeric species have been proposed to have high affinity to synapses of subsets of hippocampal and cortical neurons causing neurotoxicity via cell surface receptors. The exact structure and localization of these toxicologically relevant oligomers and their receptors have not been characterized in human brain and a relationship between specific oligomers and the initiation of the disease has not been established jet. Up to present oligomers secreted from in vitro preparations or extracted from post-mortem brain tissue have been mostly studied , hence, it is not clear if these oligomers are present in the original brain tissue or are products of artifactual oligomerization. We reported about the localization of oligomers in neuropathologically confirmed Alzheimer disease (AD), and the relation between oligomeric densities, neuritic plaques, neurofibrllary tangles and synaptic integrity. Our results reveal that mid-range molecular weight a-beta oligomers are present in both normal aging and AD brain areas and are in strict topographic association with fibrillar amyloid deposits. In the cerebellum, despite the absence of fibrillary deposits we demonstrated the presence of oligomers in both normal aging and AD. So far, two clinical trials have specifically targeted oligomers with immunotherapy with disappointing results: Bapineuzumab binding to abeta-oligomers with low affinity for monomers as well to amyloid fibrils and Solanezumab binding preferentially to monomers. In conclusion, despite a significant amount of available knowledge on the nature and the synaptotoxic effect of a-beta oligomers, targeting specific oligomeric entities for therapy remains a significant challenge.

A proposed protocol for cognitive training when using robot programming tasks and tangible interfaces

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Abstract

This work introduces the combined use of tangible user interfaces (TUIs) and robot programming tasks as a cognitive training method for patients suffering from mild cognitive impairment (MCI). This innovative technology-enhanced method is expected to engage patients in beneficial problem solving activities, triggering their analytical and visuospatial cognitive skills. Eleven (11) patients having been diagnosed with MCI, participated in individual cognitive training sessions being engaged in robot programming tasks using the "T-ProRob" tangible interface that we developed. Both quantitative and qualitative data were recoded aiming to understand potential benefits or problems emerging from this type of activity. A significant negative correlation between 'Task Completion Time' (TCT) and patients' mental condition (MMSE index) was recorded, indicating that the time a patient needs to perform a programming task (task completion time) and the type of mistakes s/he makes might provide a measure reflecting patients' cognitive capacity for analysis and planning. We have developed (and are currently implementing) a specific patient's Programming Training Protocol (PTP), to systematically engage a larger number of patients in similar robot programming tasks. In general, the protocol prescribes up to 22 levels programming tasks of increasing difficulty. Totally, 63 tasks have been designed for the patients starting from simple linear code sequences (involving at most only 2 cubes-commands), scaling up to tasks with more cube-commands and tasks that require advanced visuospatial skills and use of more complex programming structures (like parameters and loop/control structures). Our future objective is to provide evidence on the effect that this type of training might have on patients' condition when compared also to other types of cognitive training interventions.

Next steps after ASPAD

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Absract

The aim of this project was the Augmentation of the Support of Patients suffering from Alzheimer's Disease and their caregivers. But the only unmet need is not support after the diagnosis. We have to use the latest advances in intelligent and adaptive solutions for social networks and collaborative systems. The ultimate future aim is to stimulate research that will lead to the creation of responsive environments for networking and, at longer-term, the development of adaptive, secure, mobile, and intuitive intelligent systems for collaborative work and learning. The main idea of our next project is to develop a state of the art methodology for diagnosing MCI due to AD or Parkinson Disease (PD) through easy to use and cost-effective biomarkers. The overall concept of the project is to provide better healthcare and better understanding of the biological substrates of two diseases that affect a large number of people and are currently untreatable. This will be achieved with a new diagnostic test that makes the examination faster and easier (only saliva needed). At the same time another cost effective and easy to use method, the presence of tau protein as assessed by skin biopsy, will be evaluated. Comparison of the potential of these new biomarkers with established tests will provide data concerning the pathology of AD and PD.

Project: Innovative Neuro-biological Assessment for mild cognitive impairment due to Alzheimer's disease and Parkinson's disease

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Abstract

The Innovative Neuro-biological Assessment for mild cognitive impairment (MCI) due to Alzheimer's disease (AD) and Parkinson's disease (PD) project was submitted in the framework of the Innovative Medicines Initiative 2 (IMI 2) Programme and it has the dual aim of providing insight on the biological substrates of MCI due to AD & PD while creating novel diagnostic instruments for early AD & PD detection. The project focusses on cognitive impairment, a ubiquitous symptom which can be found at both AD & PD and often heralds the onset of disease. Two new tests, a saliva test and a test based on skin biopsies will aim at the measurement of tau, Aβ42 and alpha-synuclein protein levels. At the same time Greek Crocus Sativus L will be administered to MCI patients in order to test its effectiveness as a potential therapeutic agent for AD and PD and further assess its mechanism of action. Established measures such as electroencephalogram (EEG), cerebrospinal fluid (CSF) biomarkers and standardized neuropsychological tests as well as computerized neuropsychological assessment measures will be used to assess the effectiveness of the novel tests created through this project and the therapeutic potential of Crocus Sativus. This comparison will allow for better quantification of new measures. At the same time compilation of all data from new and existing measures as well as from the assessment of the effectiveness of Crocus Sativus administration will provide insight on divergent and convergent biological substrates of cognitive impairment in AD&PD. The goal of the project is to link new scientific understanding to clinical applications and create tools that are ready for use in clinical and community medicine settings. A full report on biological substrates of cognitive impairment as well as a guide for the use of the new tests in various healthcare settings will be produced.

Project: Alzheimer's disease stem-cell treatment experimental method

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Abstract

The project Alzheimer's disease Stem-cell Treatment Experimental Method was submitted in the framework of the HORIZON 2020 EU Program and aims at utilizing autologous adipose-derived stem cells (ADSC) for the treatment of Alzheimer's disease (AD). In this project there are partners from 5 countries as Greece, Spain, United Kingdom, FYROM and Cyprus. A blinded case control study will evaluate the therapeutic potential of this method using neuroimaging techniques, biomarkers and standardized neuropsychological tests. ADSC have been used in a large number of clinical and preclinical studies, their safety has been verified and they have been approved for human use. Our choice to focus on AD was influenced by the limited effectiveness of pharmacological interventions, its enormous social and economic costs and its status as one of the leading causes of death in developed countries and by the growing potential of stem cell therapies. The proposed study will be the first clinical trial using ADSC for the treatment of AD with the aim of offering detailed insight on their therapeutic role and producing a viable treatment method for this disease. If successful this method can enter large scale clinical trials and be implemented in clinical practice. The possible development of a novel cure for a previously untreatable disease could designate Europe as an area of excellence in the development of new therapies thus attracting foreign capital and investments. At the same time the potential for economic growth in a multitude of technology and health related fields and the increased collaboration between commercial and research entities related to AD and SCs could open up new market and research opportunities.

Exploring homeostatic value of space of institutional settings for people with dementia through an environmental analogue

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Abstract
Objectives: The transition to an institutional setting can cause great distress for people with dementia. Thus, institutional settings are considered as one of the main causes of behavioural and psychological symptoms of dementia. Method: An environmental analogue - a long-haul flight - will be described to illustrate similar behavioural processes taking place in a setting for users without any cognitive, psychological or behavioural disorders.Result: The allostatic processes of this analogue are discussed to explore homeostatic value of space. Conclusion: The architectural surroundings should not be considered a mere static setting that meets the resident's physiological needs. The building's structural design can be instrumental in enhancing quality of life for dementia patients. This paper discusses how architecture of dwelling facilities for institutionalised people with dementia can positively influence psychological and behavioural processes for this population.

Alzheimer´s disease: support for family caregivers

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Abstract
The objective of this speech is threefold: First to shed some light on the contribution caregivers make to the overall care of those affected by Alzheimer's, then to give an account of the current public aid provided to these major participants in the care process, and finally to state a few demands to contribute to the progress yet to be made. One of Alzheimer's particularities is that it greatly involves the family circle of the sick. Once the diagnosis is given, the family as a whole is affected. Many of the family member's lives become fully geared toward the care of sick. In light of the costs generated, and the lack of public aid, caregivers are highly financially solicitated. They are suddenly faced with grave emotional, physical, and financial hardship. Given their contribution, aid must be provided to these caregivers. And beyond the associative scope, public authorities must face their responsibilities. A recent bill proposal discussed in Parliament shows an encouraging awareness and for the first time shows recognition of the role of the caregiver. However, this legislative breakthrough does not provide satisfactory solutions and the path is still long for the caregivers' status to be fully recognized and benefit from corresponding rights. For these reasons, France Alzheimer and related diseases works relentlessly; to put an end to daily situations of exhaustion and psychological fragility in which are thrust the caregivers.

Diabetes and dementia

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Abstract
The rising prevalence of diabetes mellitus (DM) is a great public health concern, because DM can lead to complications in several organ systems. Today, 366 million people have DM worldwide, and the number is predicted to reach 552 million by 2030. The improved life expectancy of patients with DM is likely to increase the population at risk of geriatric health complications, including cognitive impairment and dementia. Moreover, growing epidemiologic evidence has suggested that people with DM are at an increased risk for dementia development. Among elderly people, DM is associated with a 1.5- to 2.5-fold greater risk of dementia. However, the results for the subtypes of dementia are inconsistent. Notably, DM is a significant risk factor for not only vascular dementia, but also Alzheimer's disease. The relationship between DM and Alzheimer disease is less clear; while some prior studies did find an association, others did not. The varying results may be due to differences in the age, ethnicity, sex, and risk factor profile of different study populations. The mechanisms underpinning the association between DM and dementia are unclear, but it may be multifactorial in nature, involving factors such as cardiovascular risk factors, glucose toxicity, changes in insulin metabolism and inflammation. The optimal management of these risk factors in early life may be important to prevent dementia. Furthermore, novel therapeutic strategies will be needed to prevent or reduce the development of dementia in people with DM.

Dementia – Financial crisis

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Abstract
The economic crisis has significantly affected the health systems. Spending on health is declining and unable to sustain costly diseases such as dementia. The costs are passed on to private spending and the family caregiver is asked to cover the expense. In Greece, the economic crisis and reduced state health budget has led to financial measures such as increasing participation in drugs, reducing care benefits and reduced benefits for pension funds experiencing patients with dementia and their carers. But can the costs be offset by the quality of life and the value of? In this difficult economic time the country made important steps such as the creation of dementia observatory and public awareness efforts.

Managing Cognitive Impairment – Discriminations in health

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Abstract
Over the last years the increase of life expectancy has led to an increase of dementia's percentages. Dementia is a pathological condition characterized by an acquired and serious impairment of cognitive functions caused by brain damage from various causes. The mild cognitive impairment is characterized as the precocious stage of dementia. The term Mild cognitive impairment (MCI) is used to refer to an intermediary situation between normal cognitive function and possible Alzheimer's disease (AD). Prompt diagnosis is essential for efficient treatment of cognitive disorders. For this reason we use the personal record in combination with the neurological examination, the psychometrics examination with the use of user-friendly and popular tools (such as the Mini Mental test, the clock test, the test for the cognitive level, the functionality, the emotional situation and the existence or not of depressing symptoms), the laboratory tests (for anemia and vitamin B12 deficiency) and also the imaging tests such as MRI and CT scan. For the management of cognitive disorders individualized therapeutic protocols are required combined with continuous support from caregivers and relatives. But how easy is the access to healthcare for all these patients? Economical, political, social and geographical diversities of our country make access to health unequal. Although a lot of private and government owned structures are activated for the support of people with cognitive disorders and their caregivers in the big urban centers, many patients of province cannot access or afford them, leading to social exclusions and discriminations in this age group.

Cognitive Disorders: Criticism-Present-Perspectives-Conclusions

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Abstract

Critical approach of the spectrum of cognitive disorders includes comments on evidence based scientific interventions in diagnostic, preventive, therapeutic and socioeconomic frame. Until now, there is no definite proof regarding the prevention of Alzheimer's Disease (AD) or age related cognitive impairment. Research on prevention strategies is still on progress. However, adoption of lifestyle changes and possible risk factor preventive measures may have beneficial effect on cognitive disorders. Available pharmacologic therapies target on symptomatic relief by regulating the action of specific neurotransmitters. These improve cognitive and behavioral symptoms and temporarily decelerate the progress of dementia. Nevertheless, medications do not alter disease process and are effective for some but not all patients. Mean life expectancy increase implies increment of incidence as well as prevalence of dementia. Additionally, austerity measures such as health expenditure cuts, increase in the cost of prescriptions, decrease in access of public health services, premature retirement as a result of economic crisis have caused severe stress triggering the development of dementia especially in fragile populations, such as the elderly. Taking into account the increased rates of dementia, early diagnosis especially in preclinical stage, with the use of modern imaging methods and biomarkers will contribute in a more effective prevention and treatment of Mild Cognitive Impairment as well as AD. Dementia must be managed as a public health priority. A national strategic plan must be applied targeting not only in provision of high quality healthcare to patients with dementia but also in recognition of the role of careers.

Plasma metabolites as Alzheimer's Disease biomarkers

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Abstract

There is an urgent need for the identification of Alzheimer's disease (AD) biomarkers. Studies have now suggested the promise of using associations with blood metabolites as functional intermediate phenotypes in biomedical and pharmaceutical research. We have recently performed lipidomics in a sample of 35 AD patients, 40 elderly controls and 48 individuals with Mild Cognitive impairment (MCI) and employed multivariate analysis methods to identify metabolites associated with AD status. A combination of ten metabolites could discriminate AD patients from controls with 79.2% accuracy (81.8% sensitivity, 76.9% specificity and an area under curve of 0.792) in a novel test set. Six of the metabolites were identified as Long Chain Cholesteryl Esters and were reduced in AD. The levels of these metabolites followed the trend control>MCI>AD. Interestingly, we found no association between cholesterol, the precursor of ChE, and AD, suggesting that it the dysregulation of specific steps in cholesterol metabolism, rather than cholesterol itself that is responsible for these observations. We subsequently replicated these associations in an independent sample of 150 AD patients and 150 controls. Additionally, we found associations between metabolites and AD endophenotypes such as the rate of cognitive decline and brain atrophy. Our study has identified new lipid molecules, to be implicated in AD pathology and may help identify new therapeutic targets.

“Forget Me Not”: a constant struggle

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Abstract

The Cyprus Alzheimer’s Association was established in 1996 as a voluntary and non-profit making organization. It is an approved member of international organizations such as ADI, Alzheimer Europe and of course now it’s a member of Mediterranean Alzheimer Alliance. The Association is made up of a network of volunteers who support the mission and goals of the Association in all districts. I started to work as a volunteer in the Cyprus Alzheimer’s Association in 2002 and I’m a member of the committee since then. The last few years I’m the Secretary. I spend a lot of my free time working for the Association and for people suffering from Alzheimer Disease. Especially this year I spent countless hours working on various campaigns and programs we are running for the Association. More specifically I work for my district and we are running the following programs: “Home care”” program, “Peer Support Groups” to caregivers/ relatives of individuals suffering from Alzheimer’s disease with the guidance of volunteers and scientific personnel, Day Care Center, Counseling. We organized various events for fundraising and awareness during the year. Also I’m working on the European project ‘Innovage’ for the Eurocares. The main objective of the project is to develop a web platform which will include different web-based services for carers. Furthermore I worked for various campaigns we had organized for 2014 in our Association in nationwide. Such as: - The Alzheimer’s Europe campaign for the MEP’s Pledge. I have contacted all the candidates for the European Parliament and invited them to join us to the fight against the disease and make dementia a European and national public health priority and sign the pledge. 13 candidates signed the pledge and from them 2 were elected MEPs, - The public awareness campaign on the occasion of the World Alzheimer’s on 21st of September. I would like to take the opportunity to tell you more about this campaign because I believe that last year our campaign ‘Forget-Me-Not’ was the most important of all because we involve pupils of a high school and it was very touching to see the children sensitized and support the Association to raise awareness and fundraising. It all began at a first school assembly on 27th of January 2014, where our President Noni Diakou and I went and talked to both students and staff of the English School in Nicosia about the nature of the disease and its consequences on the people suffering from it, as well as their families. The students club ‘Chain of Change’ cooperated with the Association to raise awareness about Alzheimer’s disease. For the following 8 months until Saturday 20th of September 2014, when the event ‘Forget-Me-Not’ took place at the busy commercial Ledra street of Nicosia, under the auspices of the Mayor of Nicosia, the club mobilized a lot more students to think about how to raise awareness and how to bring about change in the Cypriot Society. Under the enthusiastic guidance of their teachers in charge, who cooperated with the Association, with a great sense of team spirit, pupils and teachers managed to coordinate a wide variety of events which culminated on the 20th of September in Ledra Street. The symbol of our campaign was the Lilly ‘Forger-Me-Not’ which was painted on a huge banner by the art students and was displayed on top of the Municipality parking in Ledra Street. Each of the petals of the flower was drawn to represent a theme inspired from the fight of Alzheimer Disease. The banner was kept by the Mayor of Nicosia for three weeks to help Raise Awareness. Before the event, with the help of the Association, a meeting was set up between the students and the Commissioner for Volunteerism and Non-Governmental organizations Mr Yiannis Yiannakis to present to him how the Alzheimer campaign would be set up. The Cyprus Broadcasting Corporation, state TV, was the Media sponsor and advertised the event to the radio and tv. Also we involved the president of the shops owners in Ledra Street to advertise it to the various shops. The Association informed the Multidisciplinary Committee for Alzheimer Issues of the Ministry of Health about the campaign and asked them to write a letter that would explain in simple terms to primary school children what Alzheimer disease is about and what can children do to help those in need. Once this letter was prepared, the English School students asked from the Minister of Education and Culture to circulate it to all Primary Schools to be read out on the occasion of the Word Alzheimer’s Day. This indeed happened and it is an excellent example of how the pupils have succeeded to make an impact on our society. On 18th of September we organized a musical event on the Hall of the Presidential Palace in Nicosia for fundraising and awareness. The event was held under the auspices of Mrs Andri Anastasiades, First Lady of the Cyprus Republic. In her welcoming speech, she praised the achievement of all volunteers in the Association. Musical entertainment was provided by a skilled trio (sing, piano and violin) that played a set of old songs that are still beloved by all. This was symbolic of the long term memories that people with dementia often retain and also to illustrate the important role that music can play to improve their quality of life. Our campaign culminated on 20th of September with our event on Ledra Street in presence of the representative of Minister of Health, MPs from the Health Committee, the Vice Mayor of Nicosia Municipality, the Mayor of Strovolos Municipality, the Commissioner for Children's Rights as well as Law Commissioner, the Commissioner for Volunteerism and Non-Governmental organizations, and ex European MEP. The whole event featured songs from the English School Choir, melodies by the Philharmonic Orchestra of the Cyprus Police, Art Exhibition inspired by the Alzheimer’s disease. Also the pupils organized bazaar for fundraising and we had free information material for the disease for the public. This year, although we were not able to raise money because of the Cyprus financial crisis, our campaign was a success! We managed to raise awareness among the public and to educate teachers and pupils. Our people suffering from Alzheimer were invited and many managed to participate. For all of us volunteers, the greatest reward, is the smile from our people who are suffering from Alzheimer.

Association between elderly with Mild Cognitive Impairment and Fear of Falling

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Abstract

Fear of Falling is a major health problem among elderly people and can lead to activity restriction. Objective: To identify whether old persons with Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD) could develop a subsequent fear of falling, and whether this fear of falling is associated with the cognitive, psychological and functional parameters. Methods: Forty eight (48) elderly with MCI and AD aged ≥ 50 were randomly included in the study. Fear of Falling was assessed by the FES-I a 16 item questionnaire with easy and more complex physical and social activities. MMSE and MoCA were used to assess cognitive function, FRSSD and FUCAS for function and GDS for depression. Results: 37% of the participants expressed no fear of falling, 40% expressed a little concern about falling and the rest 23% expressed a great concern. Fear of falling was associated with sex (r=.330, p=.023), age (r = .300, p= .05) and cognitive function (r = .400, p=.009). Conclusion: Among people with MCI and AD the fear of falling seems to be related with several factors as the advancing age, the female gender and the deterioration of cognitive function.

Categorization training for persons with Mild Cognitive Impairment

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Abstract

Background and aims: Categorization is a basic cognitive skill present in all activities of daily living. It is essential for memory and learning, problem solving, and decision-making. However, categorization training has not been implemented with adults with mild cognitive impairment (MCI) or early stages of dementia. The purpose of this study was to test the hypothesis that a systematic cognitive training with the Categorization Program (CP) will improve categorization abilities and neuropsychological performance in adults with MCI. Method: The CP is a systematic hierarchical starting from concrete tasks and progressing to more abstract skills. It addresses the two areas of categorization: recognition and categorization of everyday objects; and new category learning and decision making. Outcome measures include three categorization tests (CP Test 1, 2 & 3) and 4 probe tasks (to check generalization of skills) along with extensive neuropsychological battery. Ten participants with MCI and 10 healthy older adults completed the program to date (average age = 71.70, SD = 4.47; average education = 9.20 years, SD = 4.47, range = 5 - 19) completed the CP. All participants received 3-4 hours of cognitive treatment per week for 10-12 weeks. Results: MANOVA analyses resulted in significant gains on the CP Tests demonstrating improvement in the ability to describe objects (F = 21.90, p = .002) and to identify common traits between objects and extract organization rules (F = 6.56, p = .031). Participants also demonstrated significant gains in generalizing abilities to new tasks across time (F = 10.95, p = .005), which following a linear trend (F = 30.70, p = .000). Conclusions: The preliminary findings suggest that systematic cognitive training implementing the CP protocol could be a useful and feasible tool for the training of categorization skills in older adults with MCI in community settings.

Dementia caregiver burden as associated with neighbors' social capital

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Abstract

Aim: To explore the relationship between caregivers' burden with non-caregivers' perceptions of social capital. Background: There is an increasing interest in developing dementia-friendly communities that would allow people with dementia and their caregivers to live in their own homes and neighborhoods for as long as they wish and to maximize their quality of life. Social capital is an important resource that could be utilized within the community context, but little is known about dementia patients and their families from a social capital perspective. Design: A descriptive, correlational study was implemented. Methods: Seventy groups of caregivers matched to non-caregivers from the same neighborhood from 2 different cities in Cyprus participated in the study; three instruments were used to collect the data: the Zarit Burden Interview, the Centre for Epidemiological Studies-Depression (CES-D) scale and the Social Capital Questionnaire. Paired sample t-tests and correlation analysis were performed in order to examine all the hypotheses of interest. Results: Results in each pair for the overall social capital showed higher scores for the non-caregivers (Mean= 66.41) and lower for the caregivers (Mean=63.66) with significant differences for each group (t=2.09, p=0.04). The correlation between caregiver burden and social capital in the pairs showed that the overall burden score is negatively related with the non-caregivers' social capital (r= -0.353, p=0.003). Caregivers' personal strain and relational deprivation were related to low scores on the non-caregivers' social capital factor of participation in the local community (r=-0.41, p<0.001 and r= -0.30, p=0.011 respectively). Conclusion: Understanding the relation between caregiver burden and social capital will enhance health care professionals' capacity to explore social capital to the benefit of dementia caregivers in the community.

Quality of life in healthy aging

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Abstract

Background/Aims: We investigated specific domains of quality of life and demographic characteristics such as age, education and gender in a large cohort of cognitively healthy older adults. Method: A total of 578 Greek Cypriot persons aged between 60 and up to 91 were recruited in the Neurocognitive Study on Aging. Of the 578 persons assessed, 395 participants who were cognitively healthy, without significant depression, psychiatric or neurological history and met all study criteria were retained; 171 males and 224 females. Participants were administered the WHOQOL-BREF to measure quality of life using the WHO-ICF framework. Results: MANOVA yielded significant gender and education effects on most measures of QoL. Self-reports of QoL remained stable across older adulthood. Sequential stepwise regression confirmed that gender, score on GDS and years of education made significant contributions to predicting the total score on WHOQOL-BREF and accounted 31% of the variance. R^2 = .310. Conclusion: Self-reports of QoL remain stable across the life span whereas demographic variables such as gender and years of formal education affected several domains of QoL and, along with depression symptomatology, accounted for a significant part of the variance the WHOQOL-BREF. Implications for people at risk for dementia will be presented.

The level of Quality of Life of dementia caregivers and its association with depression and burden: a correlation study in Cyprus

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Abstract

Background: Caring for an individual with dementia can be a stressful experience affecting both the physical and psychological well-being of the caregiver. Quality of life measurements have mainly focused on patients and factors that influence caregivers' quality of life have not been clearly defined. The study aimed to assess the level of self-report quality of life of dementia caregivers, and how this is related to their experienced level of burden, their reported number of depressive symptoms, and the level of care-recipients' dependency. **Methods**: A cross-sectional descriptive study was carried out. Caregivers were referred and recruited from both public and private practice neurologists in Cyprus as well as community psychiatric nurses via the mental health services. Seventy-seven caregivers completed the following instruments measuring: Quality of life-Alzheimer's Disease, the Zarit Burden Interview, the Centre for Epidemiological studies-Depression scale, Activities of daily living of the patient, and demographic information. **Results**: The participants indicated a mean score of quality of life at 30.89 (SD=8.21; theoretical range 13-52). Participants also reported high levels of burden (M= 43.32/SD=15.23) and depression (59.2% scored over the cut-off point of 16). Quality of life was negatively correlated with burden (r=-32, p=0.01) and depression (r=-0.296, p<0.05). Multiple regression analysis showed that the overall burden score and income explained 20% of the overall variance of QoL. **Conclusion**: Further research is necessary to investigate which additional domains are related to quality of life and increase our understanding of the factors that reduce the level burden in dementia caregivers.

Impact of music intervention technique Music Care© in the context of Alzheimer's disease

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Abstract

Objectives: Numerous studies emphasize the application of music therapy and music intervention in the treatment of Alzheimer's disease. The music intervention that was designed at the University Hospital of Montpellier applies the U-shape music composing technique taking into account the available evidence of the literature on relaxation paradigms. The main objective of this article is to summarize recent research on the standardization and evaluation of Music Care© technique in the treatment of pain, anxiety and depression in patients with Alzheimer disease. Methods: Following a comprehensive review of the literature, a series of controlled, randomized, multi-centered studies were conducted including patients seeking care in such diverse setting as geriatrics, neurology, rheumatology, functional rehabilitation, oncology, and general pain treatment. Results: The effect of Music Care© has been evaluated on anxiety and depression in patients with Alzheimer's disease as well as different types of pain and neurodegenerative disease. Physiological effects on hemodynamic and respiratory markers as well as psychological outcomes, including the relationship between care-provider and patient have been emphasized within multiple trials. Conclusion: These results confirm the valuable effect of this music intervention on anxiety and depression in patients with mild to moderate Alzheimer's disease. Music Care© is simple to implement and can easily be integrated in a multidisciplinary programme for the management of Alzheimer's disease.

Changes in synapse in dementia: relationship to symptoms and potential therapeutic opportunities

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Abstract

Alzheimer's disease (AD) and other common dementias such as Lewy body dementias (Parkinson's disease dementia, PDD and dementia with Lewy bodies, DLB) and vascular dementia have characteristic macroscopic and microscopic pathologies. In some cases those pathologies, for example tangles in AD, are good correlates of the cognitive symptoms of the disease but this is not always the case. It is self evident that synapses are a vital part of the ability of neurons to communicate and any loss or dysfunction would have significant implications for the function of the particular brain region in which such changes occurred. This is supported by the observations that both structural markers (eg synaptophysin) and functional neurochemical markers of specific neurons (eg choline acetyltransferase activity) are often stronger correlates of cognition in AD. Much less is know about the changes that occur in synapses in other dementias and therefore the purpose of this lecture is to provide an overview of studies of synaptic integrity in AD, DLB, PDD and vascular dementia. These studies identify synaptic changes as being clinically important in terms of both cognitive and behavioural symptoms associated with dementia and provide opportunities to identify biomarkers and to develop therapeutic approaches.

Adverse outcomes and delirium in demented hospitalized patients

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Abstract

Hospitalization can be a major life-changing event with potentially catastrophic consequences for patients with Alzheimer disease (AD). Complications, including cognitive decline, increased morbidity and mortality, longer hospital stays, delirium, loss of independence, institutionalization, and death, are common outcomes that contribute substantially to the economic burden of AD. The risk for hospitalization is increased 3-fold for patients with AD. Each year, 20% to 40% of patients with AD are hospitalized for an average of 3.7 days per person-year. With increasing lifespan, hospitalization for major illness or surgical interventions will become increasingly common in older patients. Understanding the effects of surgery and anesthesia on cognitive function, is clearly a major public health issue and should be a major focus of research efforts in the future. Postoperative delirium (PD) and postoperative cognitive dysfunction (POCD) are two separate syndromes of cognitive decline after major surgery. Postoperative delirium is a common and serious complication in hospitalized elderly people. Its incidence varies from less than 10% to 50% after orthopaedic, abdominal and cardiac surgery. Delirium is associated with persistent functional and cognitive decline, increased morbidity and mortality, longer hospital stays, higher rates of nursing home placement and increased health-care costs. Mortality rates vary from 4% to 20% in patients who develop delirium during their hospital stay. It is therefore important to optimize the care for this growing group of patients. The current treatment to prevent delirium consists of pharmacological and non-pharmacological, mostly multicomponent, interventions. Both have proven effective.

Use of assessment tools for cognitive and everyday functionality: need for separation of the healthy with the pathological spectrum in these areas of examination

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Abstract

Driven by the recent political interest on healthy and active ageing, much interest has been placed on seniors' cognitive vitality and subsequently on their capacity to live independently. In this area, much attention has been paid in risk factors that lead to neurodegenerative diseases in older age (mainly various forms of dementia, stroke, and Mild Cognitive Impairment), which lead to dependency from a caregiver. Dependency or capacity for independent living has been measured so far with various instruments that assess everyday functionality. However, studies that examined thoroughly the relation between cognitive status and everyday functionality in older adults indicate that this relation is small to modest. By limiting the scope of inquiry in the cognitively challenged population, the relation between cognitive performance and everyday functionality increases and becomes modest. Despite that, the examination of the relation between cognitive performance and everyday functionality in the healthy spectrum of cognitive functionality (i.e., to cognitively unchallenged seniors) is missing from the literature. This presentation will use a critical approach in this issue, assessing the suitability of assessment tools for cognitive performance and everyday functionality depending on the population in reference. Research practices that should be avoided and others that illuminate this issue will be presented, advocating that different tools should be used in cognitive challenged and cognitively unchallenged senior. This is because research efforts that blend together samples with participants that have crossed the threshold of neuropathology with those that did not, assessing them both with tools that are either not designed specifically for detecting neuropathology, or cognitive performance in the healthy spectrum, give confusing and often misleading results. This has serious implications in clinical and research practice, which can inform this way better policy making initiatives, aiming at addressing the issue of independency in older age, in relation with cognitive health.

Social engagement and networking as determinants of cognitive and affective well-being in the silver years

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Abstract

Loneliness is an important determinant of psychological well being in the silver years. It is defined as a distressing feeling when the quality or quantity of social relationships is not meeting one's standards. Research indicates that approximately one fourth of the general population experiences loneliness as a chronic state. Lonely is strongly related to perceived social isolation, which appears to have serious consequences on physical and mental well-being. Moreover, loneliness has been associated with cognitive decline and decreased executive control, as well as with increased depressive symptoms and risk of Alzheimer's disease. The mechanism responsible for the effect of loneliness on mental health remains relatively unexplored. Several systems have been implicated, including a social bias towards threatening stimuli, which causes deterioration of emotional control. It has alternatively been suggested that self-fulfilling prophecy feeds in a self-reinforcing loneliness loop, accompanied by feelings of hostility, stress and anxiety, which in turn activate biochemical systems with consequences to physical and mental health. Social engagement and networking could act as a protective mechanism against loneliness and cognitive decline, by reducing perceived isolation and enhancing a sense of belongingness, as well as by maintaining cognitive capacity through interaction and communication.

Grandparenting as a protective factor against affective and cognitive decline

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Abstract

Grandparents play different roles in different societies according to cultural norms, religious beliefs and socioeconomic factors. In Greece, grandparents are generally viewed as a valuable source of emotional, instrumental and financial support and they help their children raise their grandchildren. The participants of the present study were 10 grandparents (6 grandmothers and 4 grandfathers) aged 63-79, raising grandchildren for a period of 3-15 years. There were 4 couples included in the study and 2 widowed grandmothers. They were interviewed about their perceived roles as grandparents and the way in which raising their grandchildren influenced their everyday lives. They all stated that it was their duty to help their children, because they worked for very long hours to make ends meet. They said that taking care of their grandchildren was demanding, but it was also very rewarding. They felt they had the chance to become parents once again and this time have the luxury to spoil their grandchildren. Grandparents argued that it helped them stay physically active, since they had to take their grandchildren out for a walk, to school or to extracurricular activities. They felt that they had a purpose when they woke up in the morning and this was more important for grandfathers who had retired from work and did not know what to do with their time. They said that grandparenting kept their minds from busy, otherwise they would be depressed. They were reading stories to their grandchildren, helping them with their homework, playing board games with them and this helped them stay alert. Some grandparents provided examples of friends who were not involved in raising their grandchildren and had become depressed (especially widows/ers) or started losing their minds. The findings are discussed in relation to the importance of involving grandparents in the upbringing of their grandchildren.

Bilingualism as a potential factor protecting against cognitive decline

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Abstract

Literature suggests that it is possible to detect a bilingual benefit in a combination of executive functions relative to monolinguals, especially in older adults, due to age-related decreases in these functions which leave room for improvements from the cognitive training of bilingual language-switching in these functions. However, the problems in replicating this benefit imply that there may be factors confounding those findings, such as differences in the socioeconomic status (SES) of the participants. In addition, the reliability of the self-reports usually employed to assess level of bilingual skill have suffered criticisms. Thus, in this experiment older adults, either bilingual or monolingual, of equally low SES were tested in the three main attention functions and the Simon effect under different WM manipulations. A language-switching task was used as an objective measure of bilingual proficiency. Results showed a bilingual benefit over monolinguals in executive attention under high WM load. Given the sensitivity of these cognitive functions to Alzheimer's disease (AD), we suggest that maybe bilingualism can work as a protective factor against the cognitive decline related to AD, but this is for future studies to investigate further.

Long term care for people with dementia- Facilities and approach of care

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Abstract

In recent years due to the fact that the average life expectancy has increased, the number of people with dementia has been observed to be of higher levels. Due to the above, the existence of specialized elderly care unit in Greece is of a major importance. Families play a key role in providing care for the elderly and people suffering from dementia. The majority of older people continue to live at home either with their families, or close to them. Moreover, many families choose to occupy a paid caregiver in order to take care of the demented person. In Greece, there is a lack of specialized long term facilities for people facing dementia. Usually long-term residential care for people with dementia is provided in private old peoples' homes and nursing homes for the chronically ill. Elderly care units specialized in people with dementia should employ experienced scientists and proficient health professionals. Nurses, Psychologist as also Social Workers and Physiotherapist, are some of health professionals who should be occupied in a regular basis in an elderly care Unit. This kind of units should provide their residents with specific services such as qualitative nursing care, medical supervision, and psychosocial interventions with a great emphasis in personalized care. To conclude, an elderly care unit, specialized in people with dementia, should goes beyond any static approach. The idea of care, including personal hygiene, healthy and tasty food, nursing and medical care and a clean environment should been taken for granted. A dynamic approach is the key that differentiates ordinary units from long - term care facilities for people with dementia. The adaptation of a holistic view, when different specialties cooperate with a main objective the quality of care but mostly the quality of life, is in the core of the dynamic approach.

Neuroimaging methods vs. lesion studies

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Abstract

The invaluable contribution of modern neuroimaging methods to the deeper and more precise understanding of the mapping and the functioning of the human brain can be documented by means of research findings that involve complex neural processes, such as language. The review of various studies presented here reveals different missions accomplished by regions in the brain traditionally correlated with specific functions, as they were mostly substantiated by lesion studies. Due to the sophisticated techniques that underlie PET and fMRI, it is possible for experimenters initially to locate the activation that follows the performance of mental tasks, and subsequently attempt to account for this emerging picture. This further explains why there are regional differences between modern techniques and lesion studies, especially with respect to language, which is such a multilateral function. Nonetheless, there have been debates among different experimental laboratories concerning the conclusions that a particular activation may imply. This suggests that the findings should be attentively replicated in order to verify the validity of the implications and eventually provide a more thorough account of brain specialization for human language.

The pathogenesis of dyslexia

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Abstract

After reviewing the most influential hypothetical trends that exist with respect to the emergence and causation of dyslexia, namely the phonological, the genetic, and the visual deficit hypotheses, coupled with the neurobiological underpinnings, it results difficult to adopt a single approach in order to locate the causal relationships inherent to the disorder. Each one of the approaches provides critical insights to the mechanisms that underlie the development of literacy skills in normally developing children and attempt to account for the factors that may be involved in the disruption of this learning process which is expected of children when emerged in literacy acquisition. The establishments of accurate phonological and orthographic representations, exposure to print, as well as familial predisposition in terms of genetics, all seem to contribute drastically to the deficient development of dyslexic children. On the other hand, neuroimaging studies are bound to shed even more light onto the backstage of dyslexic reading performance. Overall, dyslexia could be accounted for by an interactive approach within the framework of which different influences would either exacerbate or moderate the severity of the phenotype of the disorder.

Do MRI volumes correlate with financial capacity? Evidence from patients with Mild Cognitive Impairment in Greece

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Abstract

This study examines the relationship between brain structure volumes and financial capacity in patients with Mild Cognitive Impairment (MCI). Eleven patients (3 men, 8 women) with a diagnosis of MCI (Mage = 71.72, SD = 7.72; Meducation = 9.81, SD = 4.04; MMMSE = 27.81, SD = 1.53) participated in the study. The patients underwent a three-dimensional fast spoiled gradient-echo imaging (IR FSPGR). Images derived with the standard VBM procedure, using SPM software, and the volumes were obtained through ROI based extraction of the respective structures. Briefly data were bias corrected, spatially normalized onto the MNI template, segmented and modulated to account for non-linear warping. Patients at the same time underwent a neuropsychological assessment and they were examined with a new scale, the Legal Capacity for Property Law Transactions Assessment Scale (LCPLTAS). **Results** revealed numerous statistically significant positive correlations between various brain volumes and LCPLTAS scores. White matter volume correlates with performance on LCPLTAS ($r = .676$, $p = .022$), total intracranial volume correlates with LCPLTAS ($r = .630$, $p = .038$), the left hippocampus volume correlates with LCPLTAS ($r = .671$, $p = .024$), and the left parahippocampal cortex volume correlates with LCPLTAS ($r = .659$, $p = .027$).

In **conclusion**, it is not surprising that there are significant relationships between brain volumes and financial capacity in our MCI sample. Future research concerning financial capacity should focus on the analysis of conjoined neuroimaging and neuropsychological data.

Association between helicobacter pyliri infection, glaucoma and dementia

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Abstract

Aim: The aim of this study was to investigate: a) the association between *Helicobacter pylori* (*H. pylori*) infection, glaucoma and other neurodegenerative diseases (i.e., Alzheimer's disease, Parkinson's disease dementia, frontotemporal dementia, dementia with Lewy bodies) and b) the possible association of additional certain indices including Apolipoprotein-ε4 and serum ferritin, fibrinogen, homocycteine, vitamin B12 and folic acid levels with the aforementioned neurodegenerative disorders. **Patients and methods:** The following 4 groups of participants were included in this study: i) 60 patients with dementia included Alzheimer's disease, Parkinson's disease dementia, frontotemporal dementia and dementia with Lewy bodies patients, ii) 35 patients with glaucoma, iii) 31 anemic control patients without upper and lower gastrointestinal tract macroscopic lesions found to be negative for dementia and glaucoma, used for comparisons with *H. pylori*-related estimations, iv) 30 control participants recruited from an ophthalmology department, for comparisons with dementia- and glaucoma- related estimations. All patients were examined for the presence of: a) dementia by application of a neuropsychological battery consisting of the Mini Mental State Examination; the Neuropsychiatric Inventory; the Hindi Mental State Examination; and the Geriatric Depression Scale, and b) glaucoma by ocular examination based on visual acuity control, tonometry, fundoscopy and control of visual fields. The presence of *H. pylori* infection was confirmed by its detection in gastric mucosa specimens obtained by endocscopy. **Results:** The study showed correlations between: a) *H. pylori* infection and dementia patients ($p < 0.05$) and b) *H. pylori* infection and patients with glaucoma ($p < 0.05$). Regarding Apolipoprotein ε4, the findings showed: a) its increased presence in Alzheimer's disease patients, b) for the first time, its increased presence in *H. pylori* positive patients than in *H. pylori* negative patients, and c) significantly lower mean age of total group of dementia patients with Apolipoprotein ε4 combined by *H. pylori* infection than that of patient without this combination ($p < 0.05$). Likewise, the study showed increased presence of: a) glaucoma in dementia patients (Alzheimer's disease and Parkinson's disease dementia patients), and b) dementia (Alzheimer's disease and frontotemporal dementia patients) in glaucoma patients. Finally, the Alzheimer's group showed: a) positive associations with serum levels of fibrinogen, homocysteine and ferritin, and b) negative associations with serum levels of vitamin B12 and folate. **Conclusions:** The findings of the study may have important clinical impact applications for patients suffering from dementia and glaucoma.

Physiopathology of the cerebral small vessel disease: the role of homocysteine

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Abstract

Homocysteine (Hcy) is a non-proteogenetic aminoacid, intermediate product in the methionine methylation pathway, with recognized toxicity to neuronal and vascular-endothelial cells. High Hcy plasma levels (hHcy) may be the result of dietary deficits or genetic disorders. Toxic actions of hHcy involve oxidative stress, post-translational protein structure modifications (thiolation, homocysteinylation), epigenetic modifications and direct neurotoxic activity (NMDA over-stimulation). Hyper-homocysteinaimia is associated with cerebral small vessel disease (cSVD), i.e. leukoencephalopathy and lacunar infarcts. According to a sub-group analysis of the SMART-MR study (Kloppenborg et al. 2011, 2014), hHcy may play an independent to atheromatosis role in developing brain lesions and clinical findings. A proposed physiopathologic mechanism (reviewed by Lehotsky et al. 2015) is endothelial damage produced by hHcy which leads to increased cerebrovascular permeability and consequent local Hcy toxic activity to proteins and enzymes in the brain.

Synaptic dysregulation in a patient-specific human iPS-derived cellular model of Parkinson's disease

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Abstract

Parkinson's disease (PD) represents the second most common neurodegenerative disease in the aging population. Although a large number of animal and cellular models have provided insight into PD, it has been difficult to demonstrate that the implicated mechanisms also operate in affected human neurons. Patient-specific human induced pluripotent stem cells (hiPS) have facilitated the investigation of dysregulated phenotypes in vitro offering a unique opportunity to study disease pathogenesis. In this study we have characterized neurons derived from hiPS lines generated from skin fibroblasts of Parkinsonian patients that carry the dominantly inherited G209A mutation in the α-synuclein gene (SNCA) encoding the A53T mutant protein (A53TαSYN). Next generation sequencing (RNA-Seq) of mutant neurons has revealed a significant downregulation of genes involved in synaptogenesis, including transcripts encoding for i) presynaptic proteins such as SNAP-25, Synapsin 3, ALK and NRP2 and the CDC20-APC complex that is essential for the formation of synaptic vesicle clustering, ii) trans synaptic adhesion molecules of the cadherin family such as CDH13, CDH15, CDH9 and CHRNG and iii) postsynaptic proteins such as DLGAP2 and SLITRK1, 2 and 4. Another affected set of genes included members of the WNT family such as WNT1, DKK2, WNT7A and WISP1, that have been shown to induce synaptic degeneration and sensitivity to cell death, when impaired in animal models. The human mutant neurons exhibited profound sensitivity when exposed to various stress agents compared to healthy neurons suggesting defects in mitochondrial, protein degradation, oxidative stress and apoptosis. Finally, 26 out of the 53 deregulated mRNAs involved in synaptic processes have been linked to autism, schizophrenia and depression, the so called "diseases of the synapse". Overall our study reveals that the A53TaSYN dysregulation leads to synaptic dysfunction and increased susceptibility to environmental stress conditions, providing novel information regarding the mechanisms of A53TaSYN pathology and potential new targets for the development of therapeutics. Supported by the Greek General Secretariat for Research and Technology grants 2272 ARISTEIA I ParkinsonTransMed and 09SYN-21-969 Cooperation NoisePlus

Using ADVF stem cells for the treatment of Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is the most common form of dementia, affecting more than 44 million people worldwide. With increased life expectancy, this number is expected to rise in the future up to more than 135 million in 2050. In a series of preclinical and clinical investigations for the treatment of neurological diseases two main preparations containing mesenchymal cells from adipose tissue have been used: "adipose derived stromal cells (ADSC)" and "adipose-derived vascular fraction" (ADVF). ADVF is the simplest form to be used in an autologous setting, because its preparation requires minimum manipulation and its intravenous administration has been shown to be safe, if the concerns of embolism and sepsis can be controlled. The safety of these therapies has been recently underlined in a meta-analysis study (SafeCell) including 34 studies with 1012 patients with no adverse short or long time effects observed. Several recent investigations report that ADVF can be used in cellular therapies providing a functional benefit in a wide range of neurological diseases. Adipose derived stem cells, which can home into damaged brain areas, are advantageous for the recovery of brain injury in comparison to bone marrow stem cells. It has been also reported that ADVF can be used as a novel valuable therapeutic tool for chronic inflammatory diseases of the CNS. Recent preclinical evidence indicates that intravenous administration of autologous ADVF is a safe and convenient therapeutic modality that can be beneficial for the treatment of AD. However no known clinical trials considering Alzheimer's disease have been initiated. In an effort to translate the existing knowledge to clinical practice we propose here the first phase I/II clinical trial using ADVF in old adults suffering from AD. A previous case study by the entities participating in the proposed trail involving the administration of ADVF to a patient with AD demonstrated the feasibility and safety of this method and this trial aims to further assess the beneficial effects of ADVF therapy. We propose here a blinded case control study that will include 20 patients with amnestic mild cognitive impairment (aMCI), 20 patients with mild AD, 20 patients with moderate AD and 20 patients with severe AD. Each group will be divided randomly in patients who will receive the therapy and in controls. After informed

consent each study participant will have a liposuction of about 600 g adipose tissue. ADVF will then be prepared under GMP conditions, sterility, pyrogenicity and mesenchymal stem cell content will be evaluated and cells will be stored in liquid nitrogen until use. Fifty (50) million of autologous ADVF suspended in autologous serum platelet rich growth factors (SPRGF) will be administered to the treatment group of patients once every month for a 12 month period, whereas only SPRGF will be administered to controls. PET for the detection of amyloid and tau protein burden, serum and lymphocyte inflammation markers and Alzheimer's disease cerebrospinalfluid (CSF) markers will be assessed before and after the end of the clinical trial. Furthermore EEG with 256 electrodes and assessment with a neuropsychological battery suitable for each patient subgroup will be conducted at the beginning and at the end of the trial after one year.

Collecting useless items. A dementia behavioral symptom or hoarding disorder?

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Abstract

We present the case of a 76 years old man who referred to the Day Center "St. John" of Greek Association Alzheimer Disease and Related Disorders with features of dementia. Neuropsychological examination revealed mnemonic deficits and behavioral problems. During caregiver's support group, his wife mentioned patient's tendency to collect unneeded items and his unwillingness to discard them. This pattern of behavior, known as hoarding disorder (by DCM-5 Hoarding Disorder) or the syndrome of Diogenes was initially characterized as dementia-related behavioral problem and family therapy was suggested. However, during family therapy, it was revealed that patient's obsession with excessive accumulation of material possessions of dubious value and quality started many years ago when he was young. Based on newer data, initial diagnosis of dementia was discard and patient's symptoms were attributed to pseudodementia with hoarding disorder. The patient was introduced into non-drug programs and improved significantly after 4 years. Our case highlights the importance of comprehensive family history in the establishment of diagnosis of dementia and emphasizes the possibility to redefine the diagnosis and symptoms during the years of monitoring of the patient.

The course of caregivers in Alzheimer Disease

Epi Michi

Caregiver, Vet and Animal Cinic

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Abstract

Travelling through the world of dementia is a long and tough journey. One could definitely say that it's a Golgotha people have to undergo, the patient, the family and particularly the caregiver, the person who has undertaken the individual's intensive round the clock care. The caregiver is going through a stressful situation trying to realize and coming to terms with the fact that, his beloved one suffers from dementia as well as with the issues involved. Going through numerous hardships and as the disease advances, the caregiver ends up fully devoting himself into caring the loved one, but at the same time withdrawing from social activities and worsen his physical and mental health while experiencing the frustrating situation of mourning since he is aware of what is bound to happen as the end follows a somewhat predictable path

Ilion municipality community study. A multi-axial approach based on the cognitive reserve theory

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Abstract

The theory of Cognitive Reserve (Nick SCARMEAS et Yaakov STERN (2003): Cognitive Reserve and life-style, J.Cl.Exp.Neuropsychology, 25, 625-633) inspired our group (A. Solias, D. Politis, N. Degleris) to organize and train a 12-member group of volunteers (psychologists and social workers) in order to implement a primary prospective study of 580 people aged 55-85+years, who live independently in the community of ILION, Athens -GREECE. The objective was the primary detection of memory and cognition disorders, anxiety and depression. The processing of epidemiological and sociodemographic data led a) to validate of the MMSE scale under the influence of age and education level (Psychiatry 25 (4) 2014), b) to investigate the association between memory disorders/cognitive functions and depression and vice versa (forthcoming publication) and c) to estimate the prevalence of dementia and depression in urban population and the emergence of risk factors. Follow- up over four years with regular neuro-psychiatric monitoring of clinical patients in tandem with a) cognitive empowerment groups (brain stimulation program) of people with dementia and b) psychosocial support groups (CBT) in depressed patients and caregivers. The neuropsychiatric evaluation included the following tools: MMSE, 3MS, CDT, Visual Perception test, MoCA test, Test Text, Scale GDSsf and Scale BAI. The novelty of the study lies in 1) original **prospective** study and 2) experimental implementation of a new short screening test for cognitive and memory disorders. Affiliated Services and Research Areas: 1) ILION Municipality Social Service **(Solias A.)**, 2) Psycho-Geriatrics Unit of Piraeus **(Degleris N.)**, 3) Department of Psychiatry, University of Ioannina **(Skapinakis P.)**, 4) A' Psychiatric Clinic -Aigineitio Hospital. **(Politis A.)**, 5) Bayview Medical Center -JOHNS HOPKINS MEDICAL SCHOOL, Baltimore, USA **(Lyketsos C.,).** Special thanks to my fellow volunteers who applied themselves during many years of research, going on (2008-present). Volunteers Names: **Karamberi M.(in -chief),** Daliana N., Lentidaki F., Foka K., Pantelidi F., Theodoulidou Ch., Dimitriou H., Kotsampasoglou M., Kiventidi M., Marini K., Chandrinos A., Barkadou S._
The introduction of a short screening test for Major Neurocognitive

Disorder by laypeople. The psychometric properties of a legendary story

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Abstract.

The worldwide increase life expectancy makes more aged people vulnerable to some form of dementia. Many elders facing memory problems avoid seeking help in early stages. The objective of this study is to evaluate a new tool easy that can be administered by laypeople (e.g. senior center staff or caregivers) screening for cognitive decline. **Method**: This is an ongoing population based study in an urban area in Greece (municipality of Ilion). A total of 331 community dwellers (55-85+years old) attending senior centers participated voluntarily in the study and were assessed with Hagia Sophia Test (HAST), as well as the MMSE, 3MS, and CDT tests. HAST was developed so that it committed to be administered by laypeople and briefly assesses attention, concentration, memory, orientation, as well as abstract and critical thought. The test administration takes totally 6 minutes. At first we dictate the whole text (approximately 1'30"). After 5 min we demand the elder to fulfill the blank spaces (20 words in 4min) of the story. **Results:** By estimating Pearson product moment, statistically significant correlations were found between MMSE, 3MS, CDT and the HAST ranged from .487 to.372 ($p<.001$). Receiver operating characteristic (ROC) estimation of the HAST's screening value with other measures as gold standards (MMSE, 3MS, CDT), yielded Area under Curve ranged from .733 to .761. **Conclusions**: HAST represents a useful layperson screening tool that can assist in detecting cognitive deficits among the aged, including individuals without dementia.

Exploring the association between depression and major neurocognitive disorder

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Abstract

Introduction: Mood disturbances as well as impairments in memory and other cognitive functions are commonly observed in older individuals. Contrary to the cases where these clinical conditions appear independently, the diagnostic process is complicated and full of obstacles in cases where depressive symptoms are interwoven with cognitive impairments. Objective: Exploring the association between mood disturbances and cognitive impairments, as assessed by the scales GDSsf and MMSE, respectively. Methods: Cross-sectional study that included 531 participants (age > 60 years old, Mean=72.3±6.4 years) living independently in an urban region. The ratio of female to male participants was 1.7. Results: Among the participants with major neurocognitive disorder (DSM-5/ 2013) the 38,7% meets the criteria for depression, while among the participants with depression the 34,3% meets the criteria for major neurocognitive disorder. Age, education and family status appear to influence the scores of the participants in both scales. Conclusions: The present findings support the need to assess for depressive symptoms in cases of major neurocognitive disorder as well as to screen for cognitive impairments those individuals that have a diagnosis of depression. A broader clinical evaluation can facilitate the accuracy of the diagnosis and therefore improve the quality of the treatment that is provided to the target population.

High correlation between frailty variables and dementia in a cohort of older people in Crete, Greece

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Abstract

Introduction: Frailty is an emerging geriatric syndrome synonymous to sarcopenia, and lack of adaptive capacity of the organism to stressors. Its association and interrelationship with cognitive impairment is not yet fully clarified in literature. The aim of this study was to describe the incidence of frailty variables in a cohort of ambulatory geriatric population with low Mini Mental State Examination [MMSE] score in Greece. **Population study and Methods:** Eligible participants were individuals aged 60 years and above attending Primary Health Care [PHC] services of Heraklion district, screened with a low Mini-Mental-State-Examination [MMSE] score (below 23/30 or 24/30 according to their level of education). Individuals were further assessed by specialists for dementia with thorough neuropsychiatric evaluation and neuropsychological assessment. Frailty was examined using 4 items (exhaustion, weight loss, slowness, and low activity) from the instrument for Primary Care of the Survey of Health, Ageing and Retirement in Europe (SHARE-FI). **Results:** Two hundred forty one (n=240) individuals with low MMSE were identified and among them 89 (41%) individuals were diagnosed with probable dementia. The remaining participants were assessed as normal (n=37, 17%) or with Mild-Cognitive-Impairment [MCI] (n=87, 41%). Regarding frailty variables, 43 (25%) participants reported exhaustion, having too little energy to do things they wanted to do during past month, 26 (16%) reported having less appetite in the last month, 24 (15%) reported slowness having difficulty walking 100 meters, while 40 (25%) reported low activity by seldom/never engaging in activities that require a low/moderate amount of energy. Participants diagnosed with dementia presented 2.4 higher odds of having less appetite (Odds-ratio [OR] 2.4; 95% Confidence-interval [CI] 0.95-6.1) and 2.5 higher odds of low activity (OR 2.5; 95% CI 1.1-5.6; p=0.031) as compared to the rest of participants (MCI and normal) after controlling for age, gender and the number of chronic illnesses.**Conclusions:** Preliminary results of the study report significant differences in the incidence of frailty variables such as appetite loss and low activity between individuals with and without dementia, indicating a possible association between frailty and dementia.

Using novel compounds for cognitive enhancement

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Abstract

As the incidence of Alzheimer's disease (AD) increases exponentially with age, the aging population across the world is experiencing a congruous increase in AD. Current pharmacotherapy on the market includes cholinesterase inhibitors and an N-methyl-D- aspartate receptor antagonist, providing symptomatic relief but not altering the progression of the disease. Modern research has focused on discovering and developing novel effective disease-modifying therapies which target the pathophysiologic cascade, aiming to delay disease onset and further slow its progression. In this review, different preventative approaches such as antioxidant and anti-inflammatory therapy will be discussed. Moreover, progress in disease-altering approaches, including stabilization of mitochondrial dynamics, tau- and amyloid-focused therapies, will be outlined, with an emphasis on currently ongoing clinical trials. Lastly, suggestions for future research, based on knowledge from research on cognitive enhancement in other brain disorders will be presented.

Alzheimer's Disease and dietary supplementation

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Abstract

Although it is well established that AD constitutes a multifactorial, chronic, degenerative disease, a simple search on the mass media will soon reveal a profusion of information and proposals of treatments with certain "magic pills" alias "elixirs" that promise miraculous results on the stopping of progression or even inversion of the disease and representing a flourishing industry. Only a small fraction of these claims, though, are supported by sound and adequate scientific research. An area where scientific proof is sound is that of caloric and/or protein supplementation of Alzheimer's patients in the process of losing or at high risk of losing body weight as it is known that weight loss is accompanied with worsening of the cognitive status. Pharmaceutical industry research is interested, among others, in the discovery and development of medical foods that is of "foods formulated for enteral taken under physician supervision, and intended to meet the distinctive nutritional requirements identified for a disease or condition". The list of substances used so far include n-3 polyunsaturated fatty acids, Gingko biloba leaf extracts, antioxidants (like lycopene, quercetin, resveratrol, curcumin, etc.), antioxidant vitamins (like β-carotene, C and E), vitamin D, certain vitamins of the B complex, selenium, aloe extracts, tauroursodeoxycholic acid(TUDCA), S-adenosyl methionine (SAM). The kind and level of available supporting evidence for each one of these substances is different and varies from experimental in vitro studies and animal models to epidemiological studies. Few are the available observational and intervention studies and even lesser the randomized control trials (RCTs) or the meta-analyses. A comparative table is briefly presented using a critical approach of the available publications. At this moment the most promising molecules seem to include Vitamin D and n-3 polyunsaturated fatty acids and possibly Vitamin E. Evidence is also presented concerning certain commercially available combinations.

The endocrinological facets of Alzheimer's disease and dementia-related disorders

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Abstract

Clinical, preclinical and epidemiological evidence suggest that the endocrine system is implicated in the pathophysiology of Alzheimer's disease as well as its clinical manifestations. Sex hormones have been involved in the regulation of neuron viability; β-amyloid and τ hyperphosphorylation and brain-penetrant selective estrogen receptor regulators may hold promise as potential treatment. Relative GH or IGF-I deficiency has been suggested as potential contributory factors to the deterioration of cognitive functions. Plasma parathyroid hormone has been associated with vascular dementia, epimers of vitamin D were found to be

related to disease status and dementia is an established risk factor for fractures. Positive correlations between serum free T4 levels and cognitive domains have been also reported. Furthermore, metabolic hormones –namely, leptin and insulin- can readily cross the blood-brain barrier and have been shown to directly affect hippocampal learning. Finally, bariatric surgery reverses increased cerebral metabolism observed in obese women. Collectively, the above evidence suggests that derangements in the sex hormone metabolism, GH axis, calcium homeostasis, thyroid axis and metabolic hormones in the context of Alzheimer's disease and dementia-related disorders may have potentially important clinical and research implications.

Driving ability in patients with cognitive disorders due to neurodegenerative diseases

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Abstract

Successful driving requires various physical and mental abilities, such as the capacities to: judge distances, simultaneously manage multiple incoming stimuli, maintain attention for long periods of time, perform sequencing skills, demonstrate immediate reaction in case of adverse events, and succeed proper interpretation of traffic signs and signals. Common neurological disorders affecting cognition, such as Alzheimer's disease (AD), Parkinson's disease (PD), Mild Cognitive Impairment (MCI), and Stroke can adversely affect the above abilities although in various degrees and combinations. In a number of studies visuospatial, attentional, executive and memory deficits have been shown to be good predictors of the impaired driving ability in patients with the above mentioned neurological disorders. While it is evident that patients with moderate to severe dementia due to AD pose a significant risk to individual and public road safety, some patients with mild AD seem still capable to drive without an increased risk of accidents. Research indicates that Performance on cognitive tests, mainly of visuospatial and attentional abilities, executive functioning and possibly memory is associated with the ability to drive safely in patients with mild AD. However, due to the moderate relationships of the neuropsychological tests with driving measures and individual variability, relying only on these tests for making recommendations regarding future restrictions in driving in patients with dementia may not be adequate and no single neuropsychological battery can consistently and reliably predict driving behavior. Ideally, neuropsychological tests should be used in combination with other measures, such as findings from neurological assessment and administration of actual or simulated road tests, to make driving recommendations. Research findings indicate that patients with MCI (a condition representing very often the predementia stage of AD) are at risk for driving difficulties although their performance on on-road or on driving simulator testing is not consistently worse than that of their healthy counterparts. Measures of mental flexibility, inhibitory control and visual attention appear to be associated with driving performance in patients with MCI. Our research results suggest that measures assessing information processing speed, visuospatial memory, balance and movement coordination and psychomotor vigilance have the capacity to predict various indexes of driving performance in individuals with MCI, namely number of crashes, reaction time, average driving speed, lateral position variation, and headway average time. In addition, we have found an association between depressive symptoms and sleep abnormalities with various indexes of driving performance, such as actual number of crashes, hits of side bars and number of speed limit violations in the MCI population. This suggests that their presence in MCI should be systematically assessed in order to implement proper therapeutic interventions that might help to improve the driving fitness of certain individuals with MCI. In PD, the presence of movement as well as cognitive disorders, behavioral symptoms and excessive daytime sleepiness. influence the performance of driving, increasing the risk of car accidents. Findings from a number of studies, including our driving simulator studies, indicate that drivers with PD need more time to initiate deceleration, have greater difficulty to stop at the proper position when approaching traffic signals, have lower speeds during driving around curves and show greater variation in vehicle lateral position when driving around curves. Cognitive measures of attention, executive and visuo-spatial functions appear to be stronger predictors than motor indexes of driving fitness in patients with PD and it is of interest that we have found very high correlations of certain subtests of the recently introduced Comprehensive TMT with average speed, speed variation and reaction time in unexpected incidents. In addition, while the UPDRS motor scores during the "on" phase are not consistently associated with the driving performance of individuals with PD across studies, we have found that Tandem Walking was a good predictor of driving performance as it was correlated with various driving indexes: average speed, speed and headway variation, sudden brakes and speed limit violations. Our findings suggest that sensitive motor measures of balance and movement coordination could serve as useful predictors of driving performance in the PD population. **Conclusion:** Several lines of research indicate that common neurological disorders affecting cognition have a negative impact on driving competence. Driving simulators which are still of little use in everyday practice, may become a promising tool for assessing driving capacities in patients with cognitive dysfunction. While definition of successful predictors of altered driving ability is still under way, there is a strong need for the development and application of thoughtful national policies that may improve individual and public road safety.

The autonomous elderly of Crete and their everyday lives: factors associated with longevity and successful aging

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Abstract

Purpose: The aim of this qualitative study is to explore the factors associated with successful aging and further contribute to the understanding of the lives of autonomous elderly that are in no direct need of help, care or support. It provides through their narratives and descriptions of everyday habits an account of their social and life experiences. **Design and Methods:** The study is based on 20 semi-structured individual interviews conducted with independent community-dwelling, relatively healthy and functional elderly, belonging to the 'oldest-old' and the 'very old' age groups (75 years and older). Twelve were men and eight women, all inhabitants of the Greek island of Crete. The elderly described their life experiences during three stages of the lifecourse: childhood, adult life and old age. The method of observer triangulation was used for data collection The interview transcripts were analyzed using content analysis. **Results:** Our data are in line with findings of previous qualitative and quantitative studies on the subject conducted in different cultural settings. Seven major themes emerged from the analysis: adaptiveness during adversity, autonomy and functionality, importance of family ties and social relations, healthy lifestyle and low stress, being active and socially involved, spirituality/religiosity, meaning in life/satisfaction with life, optimism and humor in coping with death. **Conclusions:** These findings provide insights into possible psychosocial and lifestyle factors associated with aging and longevity. Further qualitative research is needed to explore in depth these phenomena. Practitioners should identify and implement methods for assessing among older people factors associated with successful aging and therefore find ways to enhance the quality of life during old age. Additionally the findings outlined in this paper can inform the development of a culturally sensitive approach.

Brain research and advocacy - a European perspective

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Abstract

Brain disorders, including developmental, pain, psychiatric and neurodegenerative diseases, represent an enormous disease burden in terms of human suffering and economic cost. Data collected by the WHO suggest that brain diseases are responsible for 35% of Europe's total disease burden.i That burden is set to grow, mainly due to the fact that the European population is ageing. On the other hand, research in the brain sciences now holds the promise of stopping and even reversing neurodegeneration and Europe boasts clusters of excellent researchers. But if Europe is to seize these opportunities it needs to go forward on the basis of greater collaboration between countries, industry, academia and patient organisations, and it needs increased investment in the brain sciences. These goals are behind the creation of the EBC –to foster a better collaboration in order to advocate more importance to brain in European policies. The EBC formed in 2002 brought together scientists, clinicians, the pharmaceutical industry and patient organisations from all over Europe. With its member organizations, the EBC became a co-ordinating body of the European organisations representing neurologists, psychiatrists, neuroscientists, neurosurgeons and patients, as well as the pharmaceutical and medical device industries. Ever since, it has focussed much of its effort on demonstrating the need for more research on brain diseases and the importance of bringing the fruits of that research to patients in as rapid and equitable way as possible.

Neuropsychological tests

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Abstract

The process of neuropsychological assessment depends to a large extent on the reliability and the validity of neuropsychological tests. Consequently, the use of the neuropsychological tests seems to be one of the most important parts of the neuropsychological assessment. Despite the fact that in most cases the neuropsychological tests were made for research purposes, through their wide clinical practice were finally found to be appropriate diagnostic tools with various psychometric abilities. The neuropsychological tests which are applied for the diagnosis of mild and major neurodegenerative disorders concern three main axons. The first one comprises the overall assessment of the cognitive deficits through a neuropsychological battery of tests and refers to the assessment of different cognitive sectors such as executive function, language, attention, visual-spatial abilities and memory as well. The second axon includes the study of functional disorders, which assesses either directly or indirectly the complex and basic activities of daily living. This contributes to the determination of patients' functional state, which is crucial data for the differential diagnosis between mild and major neurodegenerative disorders. Finally, the third axon is related with the diagnosis of behavioral and emotional disorders such as depression and anxiety. The diagnosis mentioned above will contribute to the differential diagnosis among the different types of neurodegenerative diseases and the emotional disorders. In all cases, the use of neuropsychological tests requires from the specialist, thoroughly sense of the tests' application procedure, as well as its special neuropsychometric features, so as to precisely ensure the diagnosis, which will lead to the appropriate therapy.

Atypical and potentially reversible types of dementia and cognitive dysfunctions:normal pressure hydrocephalus

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Abstract

Normal pressure hydrocephalus (NPH) is a chronic hydrocephalus, which is not accompanied by a continuous increase of the intracranial pressure. Typical are rather spike-shaped pressure increases during the day. Clinically, the NPH manifests by the triad of gait disturbance, dementia of subcortical type and urinary incontinence. The gait disorder is described as apraxia or magnetic ataxia. The cerebral imaging shows typically ventricular dilatation (especially of the temporal horns), hyperintensities in the poles of the ventricles (transependymal CSF diapedesis) and narrowed sulci in the vertex area. As a special feature may be a discrepancy between the constricted high-fronto-parietal CSF spaces and the enlargement of the inner ventricles and basal cisterns. Improvement after Tap-Test is a prerequisite for a shunt implantation, which is the therapeutic gold standard and can cause a marked clinical improvement until a remission of the symptomatology. Negative predictors concerning the improvement in cognitive performance after shunt implantation can be a hippocampal atrophy and white matter lesions. Clinical cases will be presented to illustrate the importance of considering differential diagnosis in dementia syndromes as well as the importance of noticing the diagnostic difficulties and criteria of this treatable syndrome of dementia, which is often unrecognized. In addition it seems to be an important issue for further studies to consider the comorbidity between NPH and Alzheimer`s disease.

Limbic encephalitis - a rare treatable cause of neuropsychiatric disorders

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Abstract

Limbic encephalitis (LE) is a subacute or chronic, non-infectious inflammation of the brain, which usually occurs in adulthood with predominantly maninfestation in mesio-temporal structures. Therefore the clinical presentation is temporal lobe epilepsy as well as neuropsychiatric disorders. The LE is nosologically subsumed to the paraneoplastic neurological syndromes (PNS). Although less frequent, LE is probably one of the most severe forms of PNS. There has been a great number of publications dealing with paraneoplastic neurological syndromes (PNS) over the past years and a growing number of new onconeural antibodies have been identified. Besides the well-known intracellular onconeural tumor-associated antibodies, there is also a number of facultative pathogenetic antibodies bound to surface proteins. Serum and cerebrospinal fluid must be tested in specialized laboratories, as these antibodies are often more difficult to detect. As already mentinoned above , patients suffering from the so-called “classic” or “facultative” PNS can present a vast variety of clinical symptoms, thus the difficulty of an accurate diagnosis. Acute psychosis, anxiety or mood disorder, subacute behavioral changes, anterograde memory decline as well as dementia are among the most characteristic neuropsychiatric disorders described in LE. Especially in monosymptomatic psychiatric courses, this may delay the diagnosis and therefore poses a risk for residual neuropsychiatric sequelae. Clinical work-up and moreover therapy of patients with cognitive deficits or psychiatric conditions challenges physicians and nurses alike. Vitally stable patients would certainly profit from skilled psychiatric care, unfortunately not all hospitals possess the suitable facilities to attend to the needs of these patients. In summary, the onset of new neuropsychiatric syndromes should always include the differential diagnosis of limbic encephalitis, especially in younger adults. The diagnosis and therapy of limbic encephalitis is still a challenge that generally requires an interdisciplinary approach: psychiatric, neurological and intensive care.

Pseudo dementia in depression and multiple myeloma with heart amyloidosis. A reversible neuro-immunologic challenge?

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Abstract

Hypothesis: A Neuron Mirror Relationship between Depressive and Cognitive Disorders in later life, is usually observed, resulting by the contribution of cytokines among various others immune parameters. In addition the neurotransmission system of GABA is leading to the neurobiological linking of depression with the cognitive impairment, while glutamatergic pathway is functioning like a bridge between depression and cognitive impairment. TGF-β1 and BDNF are also involved in the above mechanism, by the participation of chronic inflammation and hyper activation of HPA axis. A case study of a 64 years old female patient suffering from Multiple Myeloma, Amyloid heart fusion and Thyroid dysfunction, the latest resulting as medical side-effect, will be presented and analyzed in relation to her emotional and cognitive impairment and her chronic over exposure to Stress Situations. Pseudo dementia mainly expressed as a Major Depressive Symptom was the dominant initial neurologic clinical sign. Learning **objectives**: - investigate the mechanism/circuits involved before the final manifestation of Pseudo dementia and Depression. - analyze how cytokines and the GABA circuit are also involved in this Neuron Mirroring Mechanism. - present a clinical case that indicates the above mechanisms’ involvement. **Skills**: -Research on the Mirror Neuron Process, the Neuron Modulation and The Neuron Analysis. Methods/Tools/ Scales: Neurologic Examination, Mini Mental scale, CT Brain scan, measurement of heavy and light chain levels, blood hormones’ analysis. Results, **Conclusions**: Pseudo dementia mainly expressed as a Major Depression Episode with cognitive impairment, had no significant response to SSRIs or to chemotherapy, the treatment of the main disease. Psychotherapy seems to be able to alter and influence the above mechanisms.

Reminiscence as therapeutic intervention to people with dementia

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Abstract

Aim: The current study tried to investigate possible improvement of patients with dementia attended to therapeutic Reminiscence program. Specifically, the aim is to find whether the cognition and behavior of people with dementia have better outcomes compared to patients with dementia who did not attend the program. **Method**: To assess the cognitive functions we used the following tests: The Mini Mental State Examination (MMSE), The Functional Rating Scale for Dementia (FRSSD), the Functional Cognitive Assessment (FUCAS), Geriatric Depression Scale (GDS), the Neuropsychiatric Inventory (NPI), the test Verbal fluency, the Rey Osterrieth Complex Figure Test (ROCFT), the Rey Auditory-Verbal Learning Test (RAVLT), the immediate and delayed story recall from Rivermead scale as well as the subscale detection on the map of TEA test. The diagnosis of dementia was conducted by the neurologist of the day centre of Alzheimer and the program also prepared in the same place by a psychologist of the company. The sample consisted of 67 participants (32 patients with dementia who attended the program and 35 patients with dementia who did not attend a program) aged 61-85. The majority of participants were female (women 66.7% and men 30.4%) while mean level of education was 7.5 years. Also all participants were reassessed the same tests after one year. In order to evaluate our hypothesis, we used the statistical program SPSS v 21 and specifically the Mann-Whitney and Wilcoxon test. **Results**: According to Mann-Whitney test statistical significant differences after one year assessment were found between the two groups in the following tests: frssd2 dressing ($p = .03$), frssd3 incontinence ($p = .006$), frssd7 personal hygiene ($p = .03$), understanding fucas ($p < 0.001$), fucas planning ($p = .01$), settlement time fucas ($p = .02$), dressing fucas ($p = .02$), ravlt3 delayed recall of words ($p = .007$), with better performing of individuals who attended the Reminiscence program. Also based on the statistical Wilcoxon test the intervention group showed significant improvement in the one year assessment concerning the mood and depressive symptoms gds ($p = .06$). Patients showed improvement in episodic memory tests rbmt2 (mean = 3.5) and apathy npi7 (mean = 1.6). **Discussion**: The therapeutic intervention Reminiscence enhances not only patient's mood and behavior but also the functionality of people with dementia. However because of the progressive nature of the disease it is difficult to notice improvement in all mental functions.

Exploration of the link between depressive symptoms and driving performance in individuals with mild cognitive impairment

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Abstract

Objectives: Previous studies indicate that depression has a negative impact on driving competence. Scope of the present research was to explore the link between depressive symptoms and driving indexes in individuals with Mild Cognitive Impairment (MCI) by applying a driving simulator experiment. **Methods:** Twenty four patients with a diagnosis of MCI were introduced in the study. The diagnostic criteria that were applied included a Clinical Dementia Rating score of 0.5 and the confirmation of cognitive impairments according to the results of a detailed neuropsychological evaluation. The presence of a valid driver's license and regular car driving served as additional inclusion criteria. The data collection included a comprehensive neurological/neuropsychological assessment and a driving simulation experiment. Depressive symptomatology was assessed with the application of the Patient Health Questionnaire (PHQ-9). Results: Depressive symptoms were associated with longitudinal driving control measures, namely average speed ($r=.570$, $p=.004$), average headway distance ($r=-.569$, $p=.004$) and headway distance variation ($r=-.564$, $p=.004$) as well as lateral driving control measures, such as lateral position variation ($r=.723$, $p<.001$) and average wheel position ($r=-.434$, $p=.034$). Also, a significant link was present with measures associated to the possibility of a road accident, such as actual number of crashes ($r=.584$, $p=.003$), hits of side bars ($r=.425$, $p=.039$) and number of speed limit violations ($r=.499$, $p=.013$). The significant association between depressive symptoms and various driving indexes remained after controlling for the role of sleepiness and cognitive functioning. **Conclusion:** Depressive symptoms appear to influence in a negative way the driving capacity of patients with MCI. Thus, their systematic assessment and the subsequent implementation of proper therapeutic interventions might help to improve the driving fitness of a subgroup of individuals with a diagnosis of MCI.

Tandem Walking as a predictor of driving performance in individuals with Parkinson's Disease

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Abstract

Background: Parkinson's disease (PD) affects in an adverse way driving competence. However, previous research indicates that UPDRS motor scores during the "on" phase are not consistently associated with the driving performance of individuals with PD. **Objective** of this work was to explore the capacity of motor tests to predict various driving indexes by applying a driving simulator experiment. **Methods**: Inclusion criteria required a valid driver's license, regular car driving, a score ≤ 0.5 on the CDR, and a score ≤ 3 in the Hoehn&Yahr scale. Twelve male individuals with PD (Age: Mean=63.75, SD=10.50) participated in the study. Data collection included: (a) a comprehensive neurological/neuropsychological assessment and a driving simulation experiment. Motor tests included: Rapid Pace Walk, Tandem Walking, and Tandem Walking with Reverse Number Counting. Driving indexes serving as outcome measures were: average speed, speed variation, headway variation, wheel position variation, number of sudden brakes, number of speed limit violations, and reaction time. **Results**: The strongest correlations were observed in the case of the Tandem Walking task. In particular, the analysis revealed the following significant correlations with the various driving indexes: average speed (r=-.72, p=.008), speed variation (r=-.72, p=.008), headway variation (r=.59, p=.045), wheel variation (r=-.60, p=.041), sudden brakes (r=-.61, p=.037), and speed limit violations (r=-.64, p=.025). Statistical significance was retained after controlling for general cognitive functioning in almost all cases, with the exception of the headway variation index. The findings for UPDRS motor scores showed only a small number of significant correlations with the aforementioned driving indexes. **Conclusions**: To the best of our knowledge this was the first study that utilized Tandem Walking as a predictor of driving performance in individuals with PD. Based on the present findings, it appears that sensitive motor measures of balance and movement coordination are useful predictors of driving performance in the PD population.

Is rapid dementia related to accelerated neuronal metabolic exhaustion?

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Abstract

Rapid dementia is defined as a dementing condition of rapid course causing the death of the individual not produced as a consequence of unrelated pathologic event up to two years after the beginning of clinical symptoms. The main causes of rapid dementia linked to neurodegenerative diseases with abnormal protein aggregates are Creutzfeldt-Jakob's disease (CJD), Alzheimer's disease (AD), Dementia with Lewy Bodies (DLB), corticobasal degeneration and frontotemporal lobar degeneration. CJD usually manifests as a rapid dementia but the course of rAD and rDLB dramatically differ from the clinical course of the corresponding typical forms of the diseases commonly progressing for more than ten years. In the present study, we have analyzed by using array gene expression the commonalities and differences in a series of selected rapid dementias including CJD subtypes MM1 and VV2, rAD and rDLB processed in parallel with typical AD and DLB cases at similar neuropathological stages. mRNA data were validated by qRT-PCR and followed by protein studies using western blotting and immunohistochemistry. Neuropathological studies centered on neuron loss, synaptic loss, and astrocyte and microglial responses where available in every case. Main focus of interest was related to energy metabolism, nucleolar stress, endoplasmic reticulum stress, oxidative stress and neuroinflammation. Present observations indicate a complex scenario of convergent altered pathways in rapid dementias caused by neurodegenerative diseases with abnormal protein aggregates but also disease-specific responses particularly aggressive in CJD.

Biological determinants of Alzheimer disease heterogeneity: prion paradigm implications

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Abstract

Extensive experimental data accumulated in prion diseases, and analyses of aging brain samples, indicate that the pathological process underlying prion diseases and Alzheimer's disease (AD) starts in isolated brain structures, and then spread through neuronal projections. This process can be initiated in transgenic mice models by intracerebral injection of misfolded proteins, and our data from prion diseases indicate that different structural conformers of pathogenic prion protein ("strains") carry unique disease phenotypes and have varying potencies to initiate and propagate the pathology. Accordingly, these findings have raised some fundamental questions in AD, including (i) whether different conformational features of beta Amyloid (Aβ) or tau are responsible for remarkably different progression rates of the disease, and (ii) whether subtle differences in the conformation of Aβ or tau may be responsible for diverse disease phenotypes. Our data indicate an extensive conformational heterogeneity of Aβ in AD, and argue for the existence of prion-like conformational "strains". The increased abundance of small oligomers of Aβ with unique conformational characteristics correlate with the rate of disease progression, suggesting that these assemblies are an important factor in propagating the disease pathology. Cumulatively, correlations between Aβ and tau structural data, genetic findings, and endophenotypic data, advance our understanding of the molecular mechanisms that govern the phenotypic diversity and variable progression rates of AD. These insights apply to other neurodegenerative diseases as well, and are critical in developing new therapeutic strategies that slow down the progression rate of Alzheimer's disease.

Determinants for disease progression in AD

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Abstract

Historically, AD has been regarded as a rather homogeneous disease. Many recent studies have acknowledged early onset, late onset or fast declining forms. Classification attempts using CSF biomarkers and neuropsychological test batteries have been suggested. However, comprehensive studies on clinico-pathological-molecular levels are lacking. Here we report results of a prospective cohort of patients with all AD forms, which were followed via phone calls each 6 months and direct examinations by a study physician every 12 months. A standard set of scales was used to record the disease progression, such as MMST, ADL, CERAD plus, UPDRS III plus a list of neurological/psychiatric and other symptoms, Sitting Balance Score, Standing Balance Score, Global Deterioration Scale (GDS) and Depression Score. MRI scans including DWI, and volumetric data set, were performed using standard protocols. Cerebrospinal fluid and blood samples were taken. A questionnaire including data on environmental and genetic factors will be developed and applied. In our cohort, polymorphisms in CST3 and EXOC3L2 as well as APOE4 absence were associated with more aggressive disease courses. A trend for BIN1 was observed. With respect to CSF tests, commonly used biomarker were not predictive for the most agressive disease course. However, proinflammatory status as reflected by increased cytokine levels in blood, was clearly assocoiated with rapid worsening of the clinical syndrome.

Evidence for a CSF biomarker signature identifying a rapid progressive subphenotype of sporadic AD

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Abstract

There is an unmet need for first preventive, that is disease-modifying, treatments of Alzheimer´s dementia (AD). However, preventive treatment calls for predictive diagnosis since novel preventive treatment options can only be offered if patients are identified during preclinical stages of the incipient AD. Per definition, a preclinical stage can not be detected by clinical tools and accordingly, patients at high risk for later AD have to be identified by biomarker guided predictive diagnostics. The presentation will demonstrate that patients with preclinical AD can meanwhile be identified within the clinically heterogeneous cohort of Mild Cognitive Impairment (MCI) with positive and negative predictive values of at least 90 % by a multiparameter biomarker approach relying on CSF dementia biomarkers, MRI volumetry and/or F18-Amyloid-PET. In view of a prevalence of approximately 20 % of preclinical AD within the MCI risk cohort the latter predictive values are clinically significant. Moreover, critical evaluation of the biomarkers Total Tau, Phospho-Tau 181, Abeta peptide 1-42 and Abeta peptide 1-40 does indicate that by means of CSF-NDD (CSF based neurochemical dementia diagnostics) a subtype of AD can be identified already during prodromal state of MCI which presents with a comparingly rapid clinical detoriation. These findings will become important for the prediction of the clinical course in individual MCI patients and for the future design of clinical therapy trials

Creation of a multidimensional website – thematic network for a holistic health promotion

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Abstract

The creation of the website is based on the application of the research proposal which was submitted at and awarded by the 25th International Conference of Alzheimer's Disease International Dementia: Making a Difference, 10-13 2010. Thessaloniki, Greece (E. Stefanatou). The website - thematic network was developed in order to contribute to the holistic promotion of physical, mental and psychosocial health.It is addressed to: Teachers, pupils and parents. School activities, health education officials. Medical Doctors of various specialities. Carers. People with mild dementia. Specialties associated with alternative approaches. It includes supporting material of information and awareness for all stakeholders. Specifically: Supporting material for teachers and pupils, interactive games of mental empowerment for the pupils as well as for people suffering from mild dementia (education - retraining). Scientific articles by medical doctors. Supporting material for the carers by psychologists, mental health counsellors. Articles by experts associated with alternative approaches. Forum for exchange of ideas.

Programs of action for dementia in the Dodecanese prefecture

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Abstract

The Day Care Center for Dementia Patients, "*Arsinoi*" of the organization "*Panacea*" has managed since 2009, the year it was founded, to establish its place between health and welfare services, not only in Rhodes but all over Greece, as a member of the *Pan-Hellenic Federacy of Alzheimer's Disease and Related Disorders*. Quantitatively speaking, it is worth noting the continuously increasing "family" size of "Arsinoi" at this day consisting of 650 examinees, who visited us for neuropsychological assessment, 145 participants in group programs, 24 participants in individual programs, and 29 patients who received home care. Qualitatively speaking, in these 6 years "Arsinoi" Day Care Center has noted significant courses of action for prevention, information and public awareness that are summarized as follows: a) Program of mental enrichment in healthy elderly population, that includes exercises cultivating numerical, spatial, perceptive, memory, executive and attentive abilities, with the use of computers. b) Program called "Memory: Information, Prevention, Care" that includes informative speeches open to the general public, as well as free of charge memory tests for people aged over 60. c) Program called "I learn about Alzheimer's disease: Why does my grandmother not remember my name?" concerning an intervention in kindergarten and primary schools of Rhodes aiming to inform children about Alzheimer's disease and its consequences to the patients as well as their family, and also to recognize and manage their own feelings for the disease. Every effort we make in the treatment of all forms of dementia is continued with patience and perseverance. The future aim of "Panacea" is founding a short-term hospitalization clinic with the purpose of offering accommodation to terminal patients and relieving relatives from the difficult task of caring. With this institution, it is believed that a comprehensive system will be structured for providing quality services of primary, secondary and tertiary care and nursing for dementive patients and their families.

Agios Nikolaos Lasithi Memorial Centre results

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Agios Nikolaos Lasithi Memory Center

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Abstract

The Memory Disorders' Center operates in the city of Agios Nicolaos from 29 August 2013. It is accomodated in the General Hospital of Agios Nikolaos. It is consisted by two people - volunteers, a psychologist and a social worker. So far it has evaluated about 50 people aged 45-80 years. As for the service provided, includes functional - mental evaluation, diagnosis of memory disorders and other cognitive functions and advisory - support of patients and relatives. For the detection of cognitive - mental functions several scales were used, IADL Instrumental Activities of Daily Living, Mini Mental State Examination or Hindi Mental Excamination, Montreal Cognitive Assessment, CERAD and Geriatric Depression Scale. Statistical control was carried in a sample of 50 people, from which 42% of were men and 58% women. The average of the age attendance was the 67th year. The main findings concerned the scale measuring the symptoms of dementia, MMSE - HMSE, showed that 14% of the beneficiaries appeared symptoms resembling to dementia (lowest score of 23-24), while 86% of had scores above the cut off 23-24 of specific scales. Regarding the measuring range depressive symptomatology, GDS to the percentage of 72% showed no depressive symptoms while 28% of subjects showed to appear amoderate depression.

Predicting response to cerebrospinal fluid (CSF) shunting for patients with idiopathic normal pressure hydrocephalus (iNPH): Reality or Utopia?

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Abstract

Treatment of idiopathic normal pressure hydrocephalus (iNPH) is challenging. It is well known that patients with iNPH experience sort-team symptom relief after shunt implantation, but the log-term effect of shutting has yielded diverging results. Many neurosurgeons were previously reluctant to treat patients with idiopathic normal pressure hydrocephalus (iNPH) because there were no reported series whit good surgical results. Additional preoperative diagnostic measures were therefore introduced to try to select those individuals who would benefit from surgery. The use of extended lumbar drainage of cerebrospinal fluid (CSF) to test for transient clinical improvement has been particular powerful for improving the surgical results. Diagnostic preoperative monitoring of the lumbar CSF pressure or the intracranial pressure (ICP) has been helpful in iNPH, although the use of ICP monitoring has remained controversial. The objective of the present study was to review the literature, to investigate the diagnostics, treatment and outcome of patients with iNPH after shunt treatment and to review our experience of managing iNPH during the 6-year period from 2008 to 2014 at Athens Naval Hospital.

Alzheimer's Disease: Strategies for disease modification with an emphasis on discovering novel molecules of natural origin possessing anti-neurodegenerative properties

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Abstract

The origin of many neurodegenerative disorders like Alzheimer 's disease (AD) lies in protein processing failures, which leads to protein aggregation and accumulation as amyloid fibrils. Abnormal accumulation and aggregation of beta amyloid (Aβ) peptide eventually lead to the formation and cerebral deposition of amyloid plaques, the major pathological hallmark in AD. The major proteinaceous component found in post mortem analyzed tissues is the Aβ peptide, mainly in the Aβ1-40 and Aβ1-42 forms. Understanding the aggregation mechanism and how to inhibit aggregate formation is therefore crucial and will have a major impact on health along with economical ramifications worldwide. In light of the suggested link between oxidative stress and neurodegeneration, it is proposed that endogenous antioxidants or dietary derived compounds may offer an ideal therapeutic regime for the prevention and even treatment of AD. In this study, we present an integrated approach towards the screening of bioactive antioxidants, putative aggregation inhibitors for the prevention, or treatment of AD. *Crocus sativus* L., a stemless perennial herb of the Iridaceae family, is cultivated in the Mediterranean region and South Asia for its red stigmas (saffron) that are used as a drug for various human health conditions, and for culinary purposes. The major *Crocus sativus* L.-derived bioactive constituents are trans- and cis-crocin-4 (TC-4 and CC-4) and crocin-3 (TC-3), trans-crocin-2 (TC-2), and other crocetin mono- and bis-ester glycoside compounds. These compounds were screened for binding with Aβ peptide employing nano-electrospray ionization (ESI) mass spectrometry (MS), where the formation of 1:1 noncovalent complexes of Aβ with TC-2, TC-3 and TC-4 was observed. Finally, *in vitro* screening was supplemented with cell viability assays using differentiated neuronal SH-SY5Y cells to assess any potential toxic effects of the selected substances. This work demonstrates that natural products may be effective in inhibiting Aβ fibrillogenesis without limiting neuronal cell viability.

Proteplytic clearance of alpha-synuclein in vivo: Novel targets in Parkinson's disease transmission

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Abstract

Recent evidence suggests that specific extracellular ALPHA-synuclein (AS) strains are implicated in the progression of Parkinson's disease (PD) pathology. It is plausible that deregulation in the normal processing of secreted AS may be a causative risk factor for PD. Thus, elucidation of the mechanisms that regulate the protein levels of extracellular AS becomes essential. Our recent work has suggested that kallikrein-related peptidase 6 (KLK6), an extracellular enzyme physiologically present in the CSF known to cleave recombinant AS is also implicated in the regulation of naturally secreted α-syn turnover (Ximerakis et al., FASEB J, 2014). Importantly, this processing appears to be inhibited by the association of secreted α-syn with lipids. Here, we sought to investigate factors and mechanisms that regulate α-syn extracellular levels in vivo. Using KLK6 knockout mice treated with soluble oligomers we show for the first time that secreted AS oligomeric species are regulated through a proteolytic cascade involving KLK6. The effect of the protease on the in vivo propagation capacity of specific protofibrilar AS species has also been examined. Our findings clearly suggest that physiologic modifications affect the biochemical behavior of secreted AS and provide novel insights into transmission mechanisms and potential targets for therapeutic interventions. The identification of a novel mechanism that would account for the turnover of extracellular AS will have important implications in designing new PD treatments and in the effort to unravel the key steps required for AS propagation. Pharmacological modulation of this pathway will target to inhibit the spreading and seeding of AS from one brain region to another, thus, reversing (at least partially) the PD phenotype.

Comparing the psychometric properties of the Raven's Educational Coloured Progressive Matrices among young children and older adults: A preliminary study

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Abstract

Recent findings have indicated a loss of cognitive abilities acquired during childhood before the appearance of clinically detectable dementia. The concept that the decline of intelligence in dementia patients causes retrogression to childhood has been proposed suggesting a comparison between developing children and retrograding elderly people. This comparison is useful as a large proportion of preclinical Alzheimer Disease (AD) patients with neurological changes do not demonstrate measurable cognitive decline on standard tests. The detection of preclinical AD could be more accurate through neuropsychological tests focused on the detection of developmental disturbances in childhood. Hence, the main objective of this study was to test and compare the psychometric properties (internal consistency, factorial and concurrent validity) of the Hellenic version of a nonverbal screening measure of general ability, namely, the Raven's Educational Coloured Progressive Matrices (CPM; Raven, 2008), between a group of individuals in early childhood and a group of elderly people. The first group consisted of 98 kindergarten and elementary school students, aged from 5 to 8 years. The second group consisted of 146 older adults, aged from 61 to 88 years. The tests administered for measuring cognitive abilities were the following: (a) the Raven's Educational CPM, (b) the Children's Category Test tapping nonverbal learning and memory, concept formation, and problem-solving abilities, (c) some subtests, tapping mainly vocabulary knowledge and phonological memory, of the ATHINA Test, which is an intelligence test battery, and (d) the Mini-Mental State Examination, which assess the cognitive status. The collected data will be processed by applying structural equation modeling techniques, in order to enable the comparison of the Raven's Educational CPM's factorial and concurrent validity among the two age groups and, consequently, the evaluation of its establishment as a screening test appropriate for detecting cognitive impairment in older adults.

Comparing the psychometric properties of the ATHINA Test among young children and older adults: A preliminary study

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Abstract

Recent findings have indicated a loss of cognitive abilities acquired during childhood before the appearance of clinically detectable dementia. The concept that the decline of intelligence in dementia patients causes retrogression to childhood has been proposed suggesting a comparison between developing children and retrograding elderly people. This comparison is useful as a large proportion of preclinical Alzheimer Disease (AD) patients with neurological changes do not demonstrate measurable cognitive decline on standard tests. The detection of preclinical AD could be more accurate through neuropsychological tests focused on the detection of developmental disturbances in childhood. Hence, the main objective of this study was to test and compare the psychometric properties (internal consistency, factorial and concurrent validity) of some of the subtests of a Hellenic test battery assessing learning disabilities, namely, the ATHINA Test (Paraskevopoulos, Kalantzi-Azizi, & Giannitsas, 1999), between a group of individuals in early childhood and a group of elderly people. The first group consisted of 98 kindergarten and elementary school students, aged from 5 to 8 years. The second group consisted of 146 older adults, aged from 61 to 88 years. The tests administered for measuring cognitive abilities were the following: (a) some subtests, of the ATHINA Test, tapping cognitive ability (verbal and visuo-spatial ability), phonological memory, and neuropsychological maturation, (b) the Children's Category Test tapping nonverbal learning and memory, concept formation, and problem-solving abilities, (c) the Coloured Progressive Matrices, which is a nonverbal screening measure of general ability, and (d) the Mini-Mental State Examination, which assess the cognitive status. The collected data will be processed by applying structural equation modeling techniques, in order to enable the comparison of the ATHINA subtests' factorial and concurrent validity among the two age groups and, consequently, the evaluation of their establishment as neuropsychological instruments appropriate for detecting cognitive impairment in older adults.

Comparing the psychometric properties of the Children's Category Test among young children and older adults: A preliminary study

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Abstract

Recent findings have indicated a loss of cognitive abilities acquired during childhood before the appearance of clinically detectable dementia. The concept that the decline of intelligence in dementia patients causes retrogression to childhood has been proposed suggesting a comparison between developing children and retrograding elderly people. This comparison is useful as a large proportion of preclinical Alzheimer Disease (AD) patients with neurological changes do not demonstrate measurable cognitive decline on standard tests. The detection of preclinical AD could be more accurate through neuropsychological tests focused on the detection of developmental disturbances in childhood. Hence, the main objective of this study was to test and compare the psychometric properties (internal consistency, factorial and concurrent validity) of the Hellenic version of a measure of higher order nonverbal abilities, namely, the Children's Category Test (CCT; Boll, 1993), between a group of individuals in early childhood and a group of elderly people. The first group consisted of 98 kindergarten and elementary school students, aged from 5 to 8 years. The second group consisted of 146 older adults, aged from 61 to 88 years. The tests administered for measuring cognitive abilities were the following: (a) the Children's Category Test tapping nonverbal learning and memory, concept formation, and problem-solving abilities, (b) the Coloured Progressive Matrices which is a nonverbal screening measure of general ability, (c) some subtests, tapping mainly vocabulary knowledge and phonological memory, of the ATHINA Test, which is an intelligence test battery, and (d) the Mini-Mental State Examination which assess the cognitive status. The collected data will be processed by applying structural equation modeling techniques, in order to enable the comparison of the CCT's factorial and concurrent validity among the two age groups and, consequently, the evaluation of its establishment as a neuropsychological test appropriate for detecting cognitive impairment in older adults.

Comparing the psychometric properties of the Mini-Mental State Examination among young children and older adults: A preliminary study

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Abstract

Although many test batteries have been developed for the early detection of dementia, a large proportion of preclinical Alzheimer Disease (AD) patients with neurological changes do not demonstrate measurable cognitive decline on standard tests. In addition, the concept that the decline of intelligence in dementia patients causes retrogression to childhood has been proposed suggesting a comparison between developing children and retrograding elderly people. Therefore, it is important population-based norms for the mental ability of older adults to be established starting from childhood. The main objective of this study was to test and compare the psychometric properties (internal consistency, factorial and concurrent validity) of the Hellenic version of a brief neuropsychological test assessing cognitive status in adults, namely the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), between a group of individuals in early childhood and a group of older adults. The first group consisted of 98 kindergarten and elementary school students, aged from 5 to 8 years. The second group consisted of 146 older adults, aged from 61 to 88 years. The tests administered for measuring cognitive abilities were the following: (a) the MMSE, (b) the Children's Category Test tapping nonverbal learning and memory, concept formation, and problem-solving abilities, (c) the Coloured Progressive Matrices which is a nonverbal screening measure of general ability, and (d) some subtests, tapping mainly vocabulary knowledge and phonological memory, of the ATHINA Test, which is an intelligence test battery. The collected data will be processed by applying structural equation modeling techniques, in order to enable the comparison of the MMSE's factorial and concurrent validity among the two age groups. This comparison will extend our knowledge of older adults and AD patients and evaluate the establishment of MMSE as a screening test appropriate for the detection of higher cognitive deficits in children.

Alzheimer Association of Heraklion, Crete – Allilegii (Solidarity)

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Abstract

The Greek Alzheimer Federation participates in the research and study of the Alzheimer's disease and related neurodegenerative diseases. The Allilegii (SOLIDARITY) Association of Heraklion, Crete, one of the 33 Associations in the Federation, is actively working towards this direction. Following a specific study and the approval of a research protocol by the Scientific Council of the University General Hospital of Heraklion, a Brain Tissue Biobank is operating in association with the Neurology and Psychiatry Clinic of the University General Hospital; namely, the Assistant Professor of Neurology of the University of Crete Mr. John Zaganas, the Professor of Psychiatry Mr. Alexander Vgontzas and the Solidarity Association of Heraklion. This Brain Biobank is associated with the Greek Biobank of Brain Diseases (Gr Bio N.N Hellas Neuro -Bio) of the Panhellenic Federation of Alzheimer Disease based in Thessaloniki and managed by Professor Magdalene Tsolaki, President of the Greek Alzheimer Association and the physician pathologist, Mr. Anestaki Doxakis. Many difficulties arise concerning the specific approach and preparation regarding information and awareness of the relatives of patients in order to authorize the Association to for the post mortem use of the brain of a patient with dementia. This action strengthens the hope and faith that the scientific understanding of all relevant neurological diseases is significantly promoted and gives value to all our efforts.

Assistive and companion robots in the frame of the RAPP project

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Abstract

Menander (c. 341/42 – c. 290 BC), a Greek dramatist and well known representative of Athenian New Comedy quoted that people should fear ageing as it never comes alone, meaning that getting older is accompanied by problems that create difficulties for every person. It is factual that ageing is coming with a number of issues like health problems, loneliness, social exclusion and luck of caregivers. Socio-economic factors, social perceptions and societal changes distress these issues even more. However, ageing is a physical process we cannot avoid but we can make it easier, more pleasurable and fruitful. RAPP (Robotic Applications for Delivering Smart User Empowering Applications, FP7 EU) is working towards this direction by creating robotic applications (RApps) that aim to facilitate the daily life of the elderly with the assistance of robotic agents. Objectives: The users primarily targeted are elderly people above 65 (65+), with the following characteristics: 1) Technology illiterates, 2) Diagnosed with MCI, 3) With physical impairments (operated for prosthesis or a hip fracture, hospitalized to recover their mobility functionality). The pilot users come from specific sites/institutions in Greece and Spain and are involved in a user requirement collection process. All of the users are independently living in their houses or near their children. Our goal is to assist them in their everyday lives through the use of new robotic-based technologies, so that they can continue independently living at home even if they have physical or cognitive disabilities. RAPP aspires to provide elderly those applications that will help them maintain communication with their family and friends, exercise, enjoy fun activities at home while at the same time enhance their attention and memory and feel safe. Families and caregivers on the other hand will be able to monitor the physical and cognitive status of the elderly, communicate with them and feel relieved knowing their beloved are safe at home. RAPP will succeed the above aspirations by offering relevant applications that could be simply downloaded from the RAPP platform to the robot agents and easily utilized by elderly, their family and caregivers. The robot agents currently involved in this process are: NAO by Aldebaran (Softgroup) and ANG-MED by INRIA. Discussion: Assistive and Companion robots demonstrate a positive impact for older people at risk of exclusion provoked by the deterioration of their physical capabilities or cognitive abilities. They have positive effects regarding the feelings and mood of elderly as they feel less lonely; their stress alleviates and their immune system response increases. Many studies report that companion robots, through their interaction with the elderly, elicit memories about the past and advance relations between elderly as well as between elderly and their family. Results: The results of the RAPP project have an important impact in many domains. First of all, the project being user driven and relying to real needs of real users brings technology closer to elder people who have problems to interact with it. The RAPP project allow people with cognitive problems to successfully perform daily activities, enhance their skills by means of memory games, assist people with mobility problems, and help elderly people to better interact with technology. Most importantly, RAPP provides developers with the necessary tools and APIs to build their own assistive robotic applications, in order to advance and improve the living of people at risk of exclusion.

From loneliness to solitude: A journey to adulthood for dementia sufferers

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Abstract

The primary caregivers of demented patients belong to the group of hidden victims of the disease. They experience loss at a variety of levels. However, loss is a vital aspect of being human. In fact, we learn more from our losses than from our gains. Any kind of loss makes us examine ourselves and forces us to discover what we need to do differently. It is in our experience of loss that we face most acutely the whole question of meaning. The torturing question “Why” brings us face to face with the deepest issues that both perplex and enrich our human spirit. This is the territory of spirituality, the search of meaning. Since our minds become cluttered with worries, regrets, negative self images, reactions and fears, we lead our true self getting buried deeper and deeper. One answer to our fragmented existence is to practice mindfulness which has the aim of keeping us in the “here and now” or “bringing our mind home”. This is the way to sort out the confusion and bring about tranquility, enabling us to focus on constructive thoughts. By relaxing our minds through mindfulness, we experience a renewed sense of self. This will bring with it identity, clarity and freedom in a cascade of revolutionary thinking. It will create a deeper state of relaxation, in a fairly short time, while reducing physical and psychological fatigue. It’s beneficial effects are numerous to relieve stress related disease, insomnia and high blood pressure. At the same time, we achieve improved posture, increased energy, enhanced understanding and empathy. We accept our patient with his/her illness. We take responsibility and leadership, providing orientation to ourselves. We react in an adult manner by relieving the whole range of our ability for affection.

Elderly living in the Community or in Institutions, in Urban or Rural Areas – Comorbidity

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Abstract

Dementia is thought to shorten life expectancy regardless of cause of death and people with dementia are twice at risk of death compared to those without dementia, independently of comorbid conditions. Parkinson's disease, insomnia, depression and other psychiatric disorders, hypertension, arrhythmias, diabetes, stroke, hypercholesterolaemia, osteoporosis, anaemia, pneumonia, prostatic hypertrophy, and incontinence have all been associated with dementia. This observational study aimed to compare comorbidity in elderly living in the community or at homes for the elderly in the urban or rural environment at the region of Heraklion, Crete. Following collection of demographic and medical history data, the MMSE/HINDI, GDS, and QoL questionnaires were completed. Comparisons were made by the $\chi 2$ test, the t-test and one-way ANOVAs using SPSS 16.0. Results currently available are preliminary as recruitment is still ongoing. Complete results will be presented at the meeting. Following informed consent, a total of 165 people have been assessed, 56 (14 in the community) males and 109 (41 in the community) females (mean age 79.4 years). In this subsample, it appears that Parkinson's disease, cardiac arrhythmias and psychiatric disorders have a statistically significant impact on intellectual and cognitive functions. All participants reported health problems, but only 71.5% took medication. The latter scored lower in the MMSE/HINDI and QoL questionnaires. Elderly on medication living in the community score lower in the GDS compared with these on no medication. There was also a correlation between taking medication and the educational level of elders living in community. Finally, in the group of participants so far studied, a tendency towards less aggressive medical interventions in dementia sufferers was observed. Special attention should be paid to untreated or undiagnosed medical conditions in the elderly with dementia.

Elderly living in the community or in institutions, in urban or rural areas – cognitive function and Quality of Life

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Abstract

Encouraging independent living and improving quality of life in the elderly is one of the key goals of social policy in Western countries. In order to avoid unnecessary institutionalization, care in the community is strengthened through the development of appropriate services, as 20% of the elderly in the community present with some sort of mental health illness. The sample analyzed here consisted of 165 elderly recruited from 4 old people's homes and 4 community centers for the elderly (34.10% male), with a mean age of 79.54 (SD = 9.96) years. There were statistically significant differences observed between attenders at community centers for the elderly and institutionalized elderly (p = 0.03), whereas cognitive function was significantly influenced by marital status, financial security, income, care at home, or having children. There were no differences in cognitive functioning found between males and females, but there was a strong association between QoL and cognitive level, with statistically significant differences between community residents and institutionalized individuals. People in the age range of 65-59 scored higher in cognitive functions but people aged 75-79 scored higher in the QoL questionnaire. Interestingly, for community residents, being cared for at home by a non-family member was associated with a higher cognitive level than being cared for by a family member. Regarding QoL and the relationship elderly people have with their carers, a statistically significant difference in QoL was found when the carer was the child of the elderly person. Community centers for the elderly should be supported and further developed as they seem to be pivotal in promoting optimal conditions for the cognitive ability of the elderly, whilst institutions should carefully look into enhancing the way their residents perceive and rate their QoL.

Urban or rural areas – resilience and life satisfaction

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Abstract

Psychological resilience should be optimal for successful ageing with or without the presence of dementia. Research in this field is, however, still in its infancy (Harris, 2006). The aim of this pilot study was to examine psychological resilience against perceived quality of life (QoL) and to look into its associations with life satisfaction, psychological well-being and mental health in elderly living in the community and at old people's homes in urban and rural Crete. This sample consisted of 165 elderly recruited from 4 old people's homes and 4 community centers for the elderly (34.10% male), with a mean age of 79.54 (SD = 9.96) years, the majority widowed (56.90%), who had completed at least 6 years of education. Mean resilience as tested by the Resilience Scale – 15 was significantly higher in men ($t = 2.58$, $p = 0.01$). Preliminary results showed strong positive associations between resilience, QoL and life satisfaction (as measured by the Satisfaction with Life Scale), whereas mental health problems were negatively associated with resilience. There were no statistically significant differences in resilience between elderly living in the community or in institutions. There were strong associations between resilience and psychological well-being (as measured by the Psychological Well-Being scale) and more specifically, positive associations were found between resilience and the PWB scale items of relating to others, self-acceptance, personal development and control over the environment. In conclusion, results so far show a strong relation between resilience and QoL, life satisfaction and psychological well-being. Resilience has been suggested to affect longevity and successful ageing (Zeng & Shen, 2010; Jeste etal, 2013), hence, promoting resilience is likely to enhance longevity and the well-being of the elderly.

Prevention and management of dementia in the current financial environment

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Abstract

Dementia syndromes are common, increasing in prevalence and are the largest cause of disability in industrialized societies. The World Alzheimer report estimated that there 35.6 million people living with dementia worldwide in 2010 (0.5% world's total population) increasing to 65.7 million by 2030. Dementia is already significantly affecting every health and social care system. It was estimated that the total costs of illness in the EU in 2008 were €160 billion (56% informal care). Direct costs (social care costs) are prominent in northern Europe while informal care (provided by families) remains the major cost component in southern Europe, a region where familial obligations to provide care remain the norm. Delayed recognition of dementia is common in community settings. It is commonly accepted that the majority of dementia patients are cared for in the primary care setting and clinicians working there do not have adequate time or possibly the diagnostic skills for in depth assessment of unrecognized cognitive difficulties. Delays of several years from first symptom presentation to clinical assessment are well documented. In high income countries a maximum of 50% of total dementia cases are being recognized in primary care, whereas in low to middle income countries, up to 90% of cases remain unidentified. All currently available drug treatments, psychological and psychosocial interventions seem to be effective in ameliorating symptoms during the early stages of dementia. Furthermore, interventions for carers may be more effective in allowing them to continue to provide care at home (to the extent of avoiding or delaying institutionalization) when applied earlier during the course of the disease. The importance of early recognition of dementia in primary care as well as the need for adequate specialist support will be discussed here, as well as the impact of early detection and management to the total illness cost.

Suicidal attempts and depression in Mild Cognitive Impairment

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Abstract

In depression, suicidal attempts are not rare. It is a worldwide problem which expands very quickly. According to World Health Organization, the last 45 years suicides have increased over 60% worldwide. Non-lethal attempts are valued to be 10 to 20 times more. Depression symptoms are common to young and elderly patients as well. The case study presented, is a 65 years old woman, with 6 years of education, who attempted to suicide 6 times so far. She is diagnosed with depression and mild cognitive impairment and takes anti- depressants and sedatives since 16 years old. According to the neuropsychological assessment, there are deficits in verbal memory, visual memory, executive function and verbal fluency, also there is difficulty to visual perception, impairment in visuoconstractional ability and to selective attention. Symptoms of depression and anxiety prevail, because of her life history. She is adopted, and found out about that when she was 14 years old, when she made her second suicidal attempt. Her foster parents abused her physically. She divorced 25 years ago and in 2010 she had a meningioma operation. She participated in non-pharmacological interventions and followed a psychological support group for depression.

Case study: Everyday functioning in mild Alzheimer's disease

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Abstract

In daily clinical practice, we often examine patients with good functional ability. However, they may have severe cognitive deficits, in accordance with diagnostic criteria for dementia. The difficulty of recognizing and discriminating patients with mild cognitive impairment from dementia patients lies in the functional independence criterion. This case study describes a 70 years old man, who was presented to day care center, with memory complaints and signs of disorientation. His clinical history was free of risk factors and his caregivers report that he was independent and functional in activities of daily life. He went under comprehensive neuropsychological assessment and he scored a lot more than 1-1,5 standard deviation (criterion for mild cognitive impairment) for his age and education in the memory tests. His diagnosis is mild Alzheimer's disease. He participated in non-pharmacological therapeutic interventions and followed medication with cholinesterase inhibitors. Follow - ups during the last 3 years show a stable condition, bringing on concerns about his diagnosis and the stage of dementia.

Prevention and intervention in the school community to promote brain health and the pupils awareness on the problems of people suffering from Alzheimer disease. Support and education of the emotional state of caregivers and retraining of people with dementia by the carers

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Abstract

The Association of Alzheimer Disease and Related Disorders of Heraklion Crete (Αλληλεγγύη, i.e. Solidarity) as part of its efforts to inform the public about Alzheimer's disease whilst paying special attention to PREVENTION and having the belief that everything is subject to EDUCATION, gets involved in primary schools of our city in order to inform children on the disease. The main aim is for them to be able to understand the changing behavior of grandparents so they can promptly and creatively address the situation in the best possible way and may even help the entire family with their behavior. **Objectives and study: Pupils:** Exploring the attitudes of pupils of different age groups (pupils in rural area schools of general education, pupils in urban area schools of general education and pupils of urban areas in schools of special education) regarding balanced nutrition, physical and mental exercise, education for the promotion of brain health and reassessment of their attitudes, studying the interaction of pupils with the important people in their lives: their grandfather and grandmother, raising awareness and informing pupils about people suffering from Alzheimer's disease and creating a positive environment to interact creatively with those people. **Caregivers and individuals suffering from Alzheimer's disease or other types of dementia:** The support of caregivers by applying a specific emotional empowerment program and their positive interaction with people suffering from the disease, implementation of the program by caregivers to people suffering and the cultivation of a positive interaction between them. **Methodology: Pupils: Implementation of a questionnaire** to the pupils **before** the implementation of the program in order to investigate the attitudes towards nutrition, physical and mental exercise. Detection of their preference in TV programs. Also, examination on whether and how they interact with the important people in their lives: grandfather - grandmother. Finally, investigation on whether they know anything about the Alzheimer disease, **Implementation of the educational program "Healthy Mind and Healthy Body"** through which there will be a configuration or possible modification of the attitudes of the pupils regarding the promotion of the health of their brain. Detailed information will be given to the pupils in the Alzheimer Disease. Finally, the pupils will be motivated by their teacher to discover creative ways of collaborating with their grandfather and grandmother, **Re-evaluation of pupils attitudes through the re-completion of the questionnaires** to assess the configuration – alteration of their attitudes, **Carers and people with dementia : Implementation of emotional empowerment strategies and education of the caregivers with specific educational material from the educational package "Healthy Mind and Healthy Body" as well as the educational package "From the ah! of love to the ouch! of the pain".** Through the educational material the carers will exercise in the recognition, expression and then management of their emotions. **Recording and conclusions, retraining of people with dementia through their carers** with the above material. **Recording and conclusions.**

Teaching and applications of memory strategies

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Abstract

As memory problems in the elderly population are increasing, there is great need for learning a beneficial way to use and apply strategies in sectors of everyday life aiming at the reinforcement of the cognitive reserve of the individual. The cognitive training interventions in memory sectors point at the teaching of strategies to the elderly who don't follow any and in the encouragement of their use in different sectors of everyday life such as shopping, appointments, names and recent events. What is going to be discussed is the memory strategies that can be taught and then be applied by normal elderly people with memory loss problems as well as individuals with mild cognitive impairment (MCI) so that they can cope with everyday demands including the recall of recent events and the memory of future ones. The results of a pilot study conducted to MCI participants has shown that the elderly who participated in a cognitive training intervention including the teaching of memory strategies showed improvement and not just stability of their cognitive status and more particularly benefitted in certain parameters of executive function.

«Aging on action» - proposal for creative aging in the Ioannina Prefecture, region of Epirus, Greece

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Abstract

This project proposes a set of actions aiming at the direction of active and healthy ageing. Consists of lectures, seminars, informative printed materials, media speeches (SMEs), workshops, building empowerment institutions (friendship clubs, social networking, creative teams e.g. dance classes, tour, etc.), lobbying and interventions at policy makers etc. These actions aim at both the general population and groups such as the elderly (60+ years), caregivers, employers, organizations that come into contact with the elderly (social Services, primary health care Centers, local government welfare services, nursing homes, etc.). The project aims to change stereotypes about aging, both in the general population and among the elderly, to remove the barriers and empower older people to overcome social exclusion, to reduce the psychological burden and prevent physical illnesses that accompany old age and finally to increase the participation of the elderly in social action. The budget of the project is 39.471,00 euros and it is sponsored by the program "We are all citizens" through the invitation "Increase of provision of social welfare to vulnerable social groups", with Bodossaki Foundation as the grant administrator. The project will be put in place in contact with the local government and other bodies of the prefecture, the church, clubs of pensioners and professional groups and generally with organizations of civil society.

NILVAD study: A European double-blind placebo-controlled phase III clinical trial of nilvadipine in patients with AD: Some preliminary findings

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Abstract

Scientific advances in the treatment of AD and drug based therapies aim at delaying the onset and the progression of this neurodegenerative disease. New promising remedies lead the way towards relieving symptoms thus saving both patients, their families and caregivers from the burden of the disease, the psychological and financial costs. Existing drug treatments proven to help patients with AD and reduce cognitive decay include rivastigmine, dopenezil, galadamine and memantine. Recently, a new substance nilvadipine, a licenced blood pressure agent, is being examined as a possible advance in the treatment of AD on a European level. The possible successful outcome of this treatment will be stabilization of cognitive decline and reduced incidence of AD, as it is expect to have both symptomatic and disease modifying benefits. Until now the preliminary findings have demonstrated that patients with mild to moderate AD present stabilization of their symptoms as well as stable performance in memory related psychometric tests. The research is still going on and the results are soon to be disseminated. The NILVAD project is a program coordinated by Trinity College in Dublin, Ireland and Kings College, London. It has 17 partners and 23 study sites taking part from 9 different countries. Preliminary findings from the data obtained by Greek patients who have terminated the recruitment will be presented by comparing patients' performance across the different psychometric tests at baseline with their performance at termination visit. **Subjects:** 500 subjects with mild to moderate AD, age range 50-90 tested over a treatment period of 18 months in a range of psychometric tests. Subjects may also participate in frailty and CSF sub-studies. **Method and analysis:** Patients with AD were assessed on a battery of psychometric tests which included: MMSE, DAD, CDR and ADAS cog administered at baseline (w0) as well as on three follow-up visits (w 13, w 52 and w78 last assessment). Any changes in cognitive functions will be assessed if a statistically significant effect in the primary outcome measure ADAS cog is found. **Recruitment:** A total of 100 Greek participants that fit the inclusion criteria for the study are expected to take part. Recruitment finishes in March 2015.

PharmaCog study: Identification of biomarkers sensitive to disease progression in patients with Mild Cognitive Impairment: a two-part clinical study. Part A. -Multisite MRI acquisition - Protocol harmonization. Part B. - Identification of biomarkers sensitive to disease progression in patients with Mild Cognitive Impairment: a clinical study

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Abstract

Mild memory problems (referred to this study as "mild cognitive impairment" - MCI) in the elderly can remain stable over time or deteriorate and progress to Alzheimer's disease. Based on current medical and scientific knowledge, we believe that the ones that will deteriorate, have abnormal imaging and biomarkers, but we must identify which specific biomarker combination provides the best results. Biomarkers are substances that can be measured in our bodies as biological status indicator, in this case as a sign of memory problems. The European project PharmaCog aims to study markers sensitive to disease progression in patients with mild memory problems. Specifically, MCI patients will be placed under study for 36 months in order to confirm the usefulness of biomarkers in the future conduct of studies which will focus on the identification and treatment of Alzheimer's disease at an early stage. **Study design.** The study is a multicentric and interventional without medication, design with two parts : Part A is performed for MRI harmonization on 60 subjects (5 in each centre, 5 subjects in Thessaloniki). Part B is performed to collect all the potential biomarkers elected on 150 subjects (total in the study and recruitment competitive), 18 patients in Thessaloniki. **Study objectives:** The Part A study objectives are to implement a “common” MRI acquisition protocol, to characterize, compare and minimize the test-retest variability across the MR sites. The part B main goals are to identify and evaluate new biomarkers of disease progression in patients with MCI by collecting biochemical, neuroimaging, neuropsychological and neurophysiological data in MCI patient with high and low CSF levels of Abeta 42. And follow those patients over time to evaluate the sensitivity for disease progression of each biomarker individually or in combination, and see how those biomarkers correlate with patients cognitive decline. **Secondary study objectives:** Develop a biomarker MATRIX which is more sensitive and predictive than the changes observed in the loss of hippocampal volume. Also harmonize the biomarker MATRIX collection and qualify multiple centres across Europe among with assessing the correlation between the biomarker MATRIX and the most accepted assessment of disease progression and conversion (Neuropsychological and CSF levels of Abeta 42).

Using a virtual reality cognitive training application for remote cognitive screening

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Abstract

Computerized cognitive training has been extensively used as an easy, enjoyable and engaging means of training cognitive functions. Its ability to be administered remotely through internet thus lowering costs has made it popular with older adults wishing to exercise their brain from the comfort of their home. At the same time computerized cognitive testing allows for easy and accurate detection of cognitive impairment with the added benefit of automated record keeping. Since computerized cognitive training cannot offer detection of cognitive impairment and computerized cognitive testing can be less appealing to older adults, as it can cause fatigue and anxiety, we have undertaken an effort aimed at addressing the shortcomings of these two different tools. Our previous study has shown that the Virtual Super Market (VSM) application can reliably detect mild cognitive impairment (MCI) with one administration following a strict administration protocol. In an effort to make regular examination of cognitive functioning more appealing to older adults we investigated the possibility of automating the process of cognitive screening using the VSM. Our goal was to provide the ability for remote screening at home, without the need for an examiner, through an enjoyable VR game-like application such as VSM. A small sample of 6 heathy older adults and 6 MCI patients used the application at home. After 4 administrations aimed at familiarizing the user with the program the software administered the program 5 times at each consecutive difficulty level for a total of 20 administrations. An analysis of the average performance of participants over the 20 administrations indicated that, despite being effected by age and education, longitudinal performance on the VSM can reliably detect MCI without the need for an examiner and a strict administration protocol. We hope these results will lead to a new model of preventive healthcare for older adults.

Physiotherapy program for the prevention of falls in patients with Dementia

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Abstract

People with Dementia very often experience falls in their daily living. Therefore, the necessity to design an efficient physiotherapy program that is based on reliable and widely used rating scales is imperative for the achievement of the best possible care of elderly people in the existing Health Care System units. The purpose of this study is to assess the efficacy of a program of physiotherapy in reducing falls in patients with dementia, aiming at improving their quality of life. We studied elderly diagnosed with initial or mild cognitive impairment who come to the Outpatients' Clinic of the Navy Hospital in Piraeus to participate in cognitive improvement programs. During taking history as a part of the clinical neuropsychological control, several patients reported incidents of falls in the recent past which inevitably cause limitations in their daily activities because of the fear of a new, possible fall. Many of them are forced to use a cane or walker in order to move safely in their home environment. For this reason, it was necessary to design intervention aimed at preventing or reducing falls. We selected 10 patients with the following characteristics: a diagnosed mild cognitive disorder (according to the MMSE test), age over 60 years and a history of falls. The participants took part in group physical therapy lasting one hour, once a week for three months. The therapeutic exercise program included exercises to improve coordination and balance, strength training of the trunk muscles, arms and legs muscles as well as exercises with simultaneous kinetic and cognitive enhancement (Dual Task Training Method). The evaluation was performed in the first week and then the fourth and twelfth week. We used for this purpose the scale described as Berg Balance Scale, which is a reliable estimation method of the dynamic and static balance of the patient during the execution of functional tests. Berg Balance Scale includes 14 tests through which we can control the ability or inability of the elderly to rise from a seat to a standing position and vice versa, the movement of the patient with or without aid and generally the functionality of the patient. The maximum score that can be achieved by each patient based on the scale is the total of 56 points, as each test is scored from 0-4 degrees, which corresponds to the highest level of functionality. Change of eight degrees indicates, based on studies carried out on the validity of the scale, a distinct change between two evaluations. All patients showed significant improvement in their static and dynamic balance. The scores obtained by Berg Balance Scale, increased from 35 points achieved on average in the first week, at 50 degrees on average, which represents an increase of 15 points after the completion of the three-month program. This improvement in the balance contributed at the same time to the enhancement of their self-confidence in the performance of specific tests. This is a key factor for the patient to participate in daily activities safely, without fear and therefore helps to the prevention of the risk of falls.

Death anxiety and religiosity in older adults

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Abstract

It is well known that the idea of death has attracted the interest of many scientific areas. Thoughts and fears related to death are able to influence a person's daily life and as a result, the quality of life. This study aimed to depict the relationship between religiosity and death anxiety in older adults. As regards the construct of religiosity, two dimensions are taken into account: spiritual and social religiosity. Spiritual religiosity refers to faith issues, such as Bible reading, praying, belief in after-life, etc. The social aspect of religiosity is more based on religious-like behaviors, such as going to church and participating in rituals. By death anxiety is determined the persistent fear which is provoked by the idea of one's own death. The aim of this study was to examine the relationships between these two dimensions of religiosity and death anxiety. Forty-seven participants, twenty-three women and twenty-four men, with age-range from sixty-five to eighty-eight (M = 73.9, SD = 6.6), filled in self-report questionnaires, in order to measure the forenamed variables. The first questionnaire consisted of fourteen questions that were especially designed in order to measure death anxiety. The second questionnaire consisted of twelve questions that examined the two dimensions of religiosity. The results pictured a relationship only between social religiosity and death anxiety: as social religiosity increases, death anxiety increases too. This relationship could be explained by the fact that people attend to church more often when the have already experienced the fear of death. Moreover, it is assumed that the absence of a relationship between spiritual religiosity and death anxiety is based on the cognitive breakdown that takes place on this age. Thus, it seems that adults appear to become more religious with age, but this could only mean that they "use" social religiosity as a mechanism to cope with the idea of death.

Quality of sleep and working memory in old adults

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Abstract

Previous research, showed that there are relationships between factors associated with sleeping, such as sleep duration, morning fatigue, insomnia and working memory. The purpose of this study was to examine the relationship between the quality of sleep and working memory in older adults. The sample consisted of 60 older adults, 30 males, 30 females. They were divided into two groups: "Young-old adults" (N=36, age range= 65-74, M=68.6) and "Older-old adults" (N=24, age range=75-87, M=79.2). Both groups were not equalized as to gender and educational level. Data about the quality of sleep were collected by a five-point scale type Likert self-reported questionnaire, consisting of 18 questions developed for the purposes of this study. The higher the score the better the quality of sleep. As regards working memory, the "Working Memory Sentences Recall" test, designed in Greek based on the working memory battery of Pickering and Gathercole (2001; Masoura et al., 2009), was administered. Analysis of variance showed that there is a significant effect of sleep quality on working memory performance. Correlations between Memory Performance and specific items of the Quality of Sleep Questionnaire showed that the feeling that they cannot sleep, the fact that they cannot start sleeping, the preference of watching TV because they do not fall asleep and the severe morning fatigue are more related to the reduced working memory performance. The results confirmed the relationships between quality and duration of sleep and working memory. Furthermore, the duration of sleep was found to be an important factor associated with memory decline in older adults. Hence, the results confirm theories and research suggesting that sleep is a crucial process for memory consolidation in old adults, since this is a cognitive process that occurs during sleep which is affected by aging-related processes.

Evaluation with CD and cellular assays of new aggregation inhibitors of the β-amyloid peptide of Alzheimer's disease

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Abstract

Neurodegeneration in Alzheimer's disease (AD) is strongly associated with the aggregation of β-amyloid peptide (Aβ) either in soluble oligomers or in insoluble amyloid fibrils. Circular dichroism spectropolarimetry (CD) is the ideal method to monitor the aggregation process of Aβ in solution as it undergoes conformational changes from monomeric, to β-sheet oligomeric, and eventually to higher β-sheet pre-fibrillar forms, ending in formation of amyloid fibrils. CD is therefore frequently employed in the search of agents that intervene with the Aβ aggregation process as potential therapeutic agents against AD. In this work two peptides isolated from biosynthesis and high-throughput genetic screening were studied with CD for their ability to inhibit the aggregation of Aβ(1-40) and Aβ(1-42) and they were both found to interact with Aβ and to modify its aggregation course. The CD results were confirmed with the thioflavin T assay that detects the presence of amyloid fibrils. Furthermore, the potential of these peptides to reduce the Aβ induced toxicity in U87MG neuronal cells was investigated and they were both shown to exert a rescue effect in cell cultures, apparently due to inhibition of Aβ aggregation into toxic oligomeric or polymeric forms. Both CD and cellular assays indicate that the peptides studied hold promise for further investigation as therapeutic agents against Alzheimer's disease.

The prognostic value of the number of cutan neurofibromas in neurofibromatosis

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Abstract

Objective: Neurofibromatosis (NF) is one of the most common inherited conditions (incidence 1/3000 births). It is characterized by the presence of cutan neurofibromas, freckling, cafe au lait spots, bone deformities and Lisch nodules in the eye (Riccardi-criteria). Greater likelihood for developing tumors is an important feature of the disease. The authors established the National Neurofibromatosis Registry of Hungary in 2011 with the aim of better understanding the pathomechanisms of NF. In the current research we investigated the possible associations between the external, visible manifestations and the presence of brain tumors and optic gliomas. **Subject and Method**: We selected patients from our database who have been examined with brain CT or MRI-scans. 53 patients were enrolled in our study, 31 persons were tumor-free. Criteria for tumor positivity (22 patients) were the histological confirmation or expansive lesions or infiltration seen by neuroimaging. We statistically related the number of visible neurofibromas – cutan tumors, Lisch-nodules, freckling, café au lait spots and bone deformities - to the number of brain tumors and optic gliomas. **Results**: 91 brain tumors were identified in 22 patients. 85% of the tumors was intracerebral. In 15% of the tumors optic gliomas were idenfied. The number of visible cutan neurofibromas showed significant difference between the tumor positive and negative groups. The chance of tumors was higher in the patients having less neurofibromas. **Conclusion**: More frequent application of neuroimaging and careful clinical examination are required in NF patients with low number of cutan neurofibromas.

Trait and state anxiety in older adults with MCI

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Abstract

Mild Cognitive Impairment (MCI) is a recently diagnostic category which includes mild impairment in the daily cognitive functioning of older adults and refers mostly to their mnemonic ability. There are many studies that have examined the anxiety of patients with MCI and have concluded that it is relatively higher than the anxiety of healthy controls. The aim of this study was to examine the levels of both trait and state anxiety of patients with MCI, compared with their healthy peers. Fifty older adults, aged from 65 to 85 years, were divided into two groups: The experimental group was consisted of 25 people diagnosed with MCI whereas the control group was consisted of 25 healthy older adults. The two groups did not differ significantly in age, gender, and educational level. Trait and state anxiety were examined using two questionnaires developed for the purposes of this study. Each one of them consists of 21 questions. The answers were given on a 4-point Likert scale. The results indicate that the two groups did not differ significantly in trait and state anxiety. In other words, it seems that MCI patients do share the same levels of anxiety with healthy older adults. Hence, their mild impairment appears to do not cause increased stress to them. So, it seems that older adults are capable to handle such a condition. In order to find the social-environmental factors that could affect their ability to adapt to MCI conditions, research should focus on how MCI patients interact with the family environment.

The effectiveness of mental empowerment program and psychotherapy on a patient with poor social network

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Abstract

X. is a 72-year-old man. He is a retired physician and diagnosed with Alzheimer's disease. The patient was married and lived with his wife until the time of her death. After his wife's death, he lived alone with a licensed practical nurse. **Case analysis and intervention plan .** X. was diagnosed with Alzheimer's disease. The patient underwent a clinical neurological evaluation, neuropsychological assessment battery, magnetic resonance imaging, laboratory studies and a clinical interview. The diagnosis was made by consensus among a neurologist, a neuropsychologist, and a psychologist. During the neuropsychological evaluation the following tests were administered: Mini-Mental State Examination, Clock drawing test, GDS and verbal fluency. The Mini Mental test result for X. was 24/30. After his wife's death, it was impossible for him to live an independent life. He was unable to move outside his house, never cooked and did very limited household activities. However, he was capable of managing his own finances, even with some problems. His children managed to hire a nurse in order to provide him help. This would enable him not only to be safer than living by his own, but also attending some treatment for Alzheimer's disease. The medication used was benzodiazepines for the symptoms of anxiety and the sleeping disorders and donepezil as blockers of acetylcholinesterase. Apart from his medication, X. received an intensive combined program for cognitive rehabilitation and mental empowerment, which would help him improve his cognitive functions and have a better quality of.Treatment consisted of a combination of direct re-training and training in activities of daily living. Overall, the patient was corrected when he made mistakes and he was provided with the correct answers in order to make him monitor his task performance and to prevent him from learning incorrect information. Direct re-training consisted of engaging the patient in several types of exercise. He was trained on tasks such as copying pictures, naming animals or recognizing similar pictures in an array of different pictures. Attention exercises involved searching for a specific letter in an array of letters, cancellation tasks, card sorting etc., while language was exercised with phonetic and semantic fluency exercises where the patient was asked to name items from various semantic categories, such as tools, fruits, names, countries etc. Visuospatial ability exercises comprised of drawing designs to copy, searching for a hidden object in an array of objects, estimating distances and similar tasks. Memory was exercised with short-term memory tasks such as remembering a string of letters or numbers and prospective memory exercises. Semantic memory was also trained by asking the patient to retrieve geographical and historical information. Finally, the ability of conceptualization was exercised by using analogies, discussing the content of a paragraph where current facts were described. Among the activities of daily living, he was asked to count money, interpret a newspaper or magazine, read an article, look for a name in the telephone directory and similar tasks. One year later, X. was more independent. His memory was improved and his medication changed. His attention ability was sharper and he coped effectively with the daily activities. The Mini Mental test score was 26/30. **Overall** it can be said that Mr X. benefited from this treatment plan, which is still continued. It was proven that the influence of Mental Empowerment and Integrative Psychotherapy – with the appropriate medication - in people with dementia is of great importance and capable of improving these people's quality of life.

The effectiveness of combined group intervention on cognitive and social skills of a patient with Alzheimer

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Abstract

Mrs. M. is a 69-year-old woman who presents symptoms of forgetfulness. She has trouble remembering names and the location of certain keys on her computer. Sometimes she can't even cook as she confuses the ingredients of the food. Her past medical history includes uncomplicated shingles and treatment with prednisone for temporal arteritis between the ages of 65 to 67, with residual osteoporosis. There was no family history of Alzheimer. **Case analysis and intervention method.** Mrs M. was diagnosed with Alzheimer's disease. The patient underwent a clinical neurological evaluation, neuropsychological test battery, magnetic resonance imaging, laboratory studies and a clinical interview. The diagnosis was made by consensus between a neurologist, a neuropsychologist, and a psychologist. During the neuropsychological evaluation the following tests were administered: Mini-Mental State Examination, Clock drawing test, GDS and verbal fluency. The Mini Mental Test score was 25/30. Her clock drawing was impaired in that she had put in at least 15 numerals and appeared insecure about how to place the hands of the clock. Mrs M. is single without children but has two nephews with whom she is very close. It was her nephews who worried about the changes in their aunt's behavior and convinced her to visit the doctor. As her nephews stated, although she used to be

polite and calm, she lately appeared to be aggressive and worried with everything. Doctor recommended her to receive memantine and donepezil. At the same time she started participating in a program of mental empowerment and cognitive rehabilitation, specifically designed for patients with Alzheimer. The structure of this program was focused on improving the deficits of their cognitive functions and their quality of life. Mrs M. was trained to language functions (semantics, phonology, naming, verbal flow and power, narrative writing e.t.c). Attention exercises involved searching for a specific letter in an array of letters, cancellation tasks, card sorting etc. Memory was trained with short-term memory tasks such as remembering a string of letters or numbers and prospective memory exercises. Semantic memory was also trained by asking the patient to retrieve geographical and historical information. urthermore, she participated in group activities in order to improve her social behavior. After a period of nine months Mrs M. appeared more confident. Her memory and attention were improved and her medication was altered. She was able to cook as easily as in the past. The Mini Mental Test score was 27/30. Meanwhile she was so connected emotionally with other participants of the program that she never missed a session and started going out with them. It was proven that the influence of Mental Empowerment with the appropriate medication in people with dementia is capable of improving these people's quality of life and their cognitive functions.

Geriatric Anxiety Inventory

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Abstract

Introduction: Geriatric Anxiety Inventory is a tool specifically designed to assess anxiety symptoms in elderly and not to diagnose specific anxiety disorders. The tool is short and easy to use and do not appear to be affected by low education or neurodegenerative disorders. Questions include little physical symptoms associated with stress, thus eliminating overlap with symptoms resulting from general medical conditions. **Aim**: To evaluate the validity of the Geriatric Anxiety Inventory as an anxiety symptom assessment tool to the elderly Greek population in relation to the test criteria which have been included (GDS, MINI, PSS) and to assess the tests' ability to discriminate the elderly with anxiety symptoms, from elderly without symptoms. **Method**: The study included 129 elderly people, 102 women and 27 men, who met the criteria for Mild Cognitive Impairment and were classified into two groups, an experimental and a control one. The experimental group consisted of 73 patients with symptoms of anxiety, according to PSS test, with an average age of 69.94 (7.38) years and an average education of 11.53 (3.97) years, whereas the control group consisted of 56 patients without anxiety symptoms, with an average age of 72.53 (6.39) and an average education of 12.30 (4.01) years. The groups were matched in age, education and mental function. **Results**: Geriatric Anxiety Inventory is correlated with the tests criteria which have been used in the study and can discriminate adequately patients with anxiety from patients without anxiety with a sensitivity of 75.3% and a specificity of 58.9%.

Intervention therapy in Progressive Supranuclear Palsy

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Abstract

Progressive Supranuclear Palsy (PSP) is a neurodegenerative disease which is often confused with Parkinson's disease due to their common clinical symptoms. Because of its rarity, PSP is not widely known to general population. Patients with PSP are often treated in the Memory Center of the Naval Hospital in Piraeus, Athens. For that reason it has been considered critical to design a physiotherapy program for these patients in order to improve their quality of life. This program enrolled 10 patients with the following common characteristics: years of age above 60, and diagnosis of PSP syndrome during the last 2 years. During the running of the program the patients received physiotherapy treatment for one hour per week for three months, and all patients were evaluated in the first, the fourth and the twelfth week of the program. The physiotherapy program consisted of specific exercises for the prevention of stiffness, exercises for the improvement of body coordination and balance (Tinetti test), as well as exercises of practicing everyday needs. Upon completion of the program, the results observed were the improvement and maintenance of a flexible neuromuscular body, improvement of the patients' everyday skills as well as improvement in their quality of life in general.

Screening of dysphagia in Parkinson's Disease

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Abstract

One of the most prominent motor and sensory symptoms of Parkinson's Disease (PD) is dysphagia, that can implicate ability of eating, drinking and pill swallowing. Timely identification of dysphagia can reduce adverse outcomes and complications for patients' heath and quality of life. This study aims to examine dysphagia in people with PD, through the implementation of screening tools and correlate findings with other indicators of the disease progression. Men and women of varying stage, duration and severity of PD, that were seen at the Neurological Clinic of the Naval Hospital of Peireus during a period of six months participated in this cross-sectional study. Patients were clinically evaluated with the swallowing of 150ml of water and swallowing speed (ml/sec), swallowing volume (ml/swallow) and swallowing duration (sec/swallow) were recorded. At the same time, masticatory ability was evaluated with a cracker and speed, masticatory cycles and duration was recorded. A control group, matched for gender and age was also evaluated. Findings are discussed and correlated with factors, such as the staging, duration, severity of the disease, cognitive status, as well as with self reported difficulties for eating, drinking and swallowing, suggesting the need for a more timely evaluation and intervention in swallowing difficulties in Parkinson's Disease.

Intervention program for patients with Multiple System Atrophy

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Abstract

Case Study Analysis. G. is a 71-year-old man, diagnosed with Multiple System Atrophy – MSA, three years ago. He is a retired accountant in occupation, who lives in the center of Athens with his wife, in the last 40 years. The patient has two sons and three grand children, with whom he spends a lot of time daily. Multiple system atrophy (MSA) is a degenetative neurological disorder, characterized by parkinsonian, cerebellar and pyramidal features along with autonomic dysfunction in different combinations, that can highly affect speech and movement. The patient in time of six months has been under the monitoring and treatment of the scientific team consisted of a neurologist, a physiotherapist, and a speech and language therapist.The intervention plan includes drug treatment, physiotherapy and a speech and language therapy program maximizing and strengthening movement and speech potential. The patient has been clinically evaluated through several tests from each specialization of researchers. More specific and concerning the physiotherapy part, there were tests conducted about the Degree of a patient's Disability and tests about the Rating of Parkinson's disease. During Speech evaluation, the patient has been clinically evaluated through tasks assessing potent disorders of speech and swallowing. Oral-motor examination has been conducted for the evaluation of the structural and functional integrity of the oral motor mechanism, as well as the Frenchay Dysarthria Assessment -FDA-2,[3] has been applied for the evaluation of the presence and characteristics of dysarthria. **Clinical Findings.**After physiotherapy evaluation it occurs that the patient exhibits upper and lower limb tremor, slowness of movement and rigidity in all muscle groups. Speech and language evaluation revealed a mixed type of dysarthria. In particular, the patient presented bilateral face and tongue weakness, slow rate of speech, hoarse voice quality, hypernasality, and reduced range of respiration. No findings of swallowing disorder were presented. **Intervention plan.** The physiotherapy program introduced techniques for body relaxation, stretching of muscles, exercises for improving body balance and general fitness, as well as a program for improving the patient's everyday necessary tasks. Speech therapy program consisted of oral - motor exercises of muscle strengthening; lips, tongue and jaw, to achieve functional articulatory integrity, phonation exercises to achieve clarity and steadiness of phonation, speech resonatory exercises and breath control techniques. **Results.**Overall it can be said that G. has benefited from this treatment plan, which is still continued. The results observed include improvement and maintenance of a flexible muscular body, as well as improvement of the patient's general abilities. Moreover, it is highly noticed that functional integrity of articulators is well maintained, speech rate has improved, respiratory management has improved, and the patient's oral communication has improved.

Example of intervention plan on functional-motor level for improved functioning in everyday tasks (ADL) in patients with dementia and Parkinsonian symptoms

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Abstract

Quality of life among patients with combined dementia and PD symptoms is highly restricted, as their ability of coping with simple everyday activities gradually declines. During the intake process at the Day Center of the Piraeus Naval Hospital, it was noticed that many patients stated to be highly dependent on their carers, even for the simplest everyday issues, which results on lower self-esteem. As a result, the application of an intervention plan was essential in order to increase the patients' independence and improve their quality of life. Five patients aged 65-75 with mild dementia and light PD symptoms were selected to participate to a program of weekly group physiotherapy sessions lasting one hour, for three months. The participants were assessed at the start of the intervention, with the use of the Barthel-Index Scale, where the majority of the patients got 55-65 points out of 100. Additional assessment took place on weeks 5 and 12. The intervention program included empowerment exercises focused on everyday needs, coordination and complex movements programming exercises, as well as practicing everyday activities (ADL). Upon completion of the intervention, patients scored 20-25 points higher on the Barthel-Index Scale, while they were more involved in everyday tasks, as was confirmed by the carers.

The role of integrative therapy on a patient with Alzheimer disease and cerebrovascular lesions (mixed type Dementia)

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Abstract

A. is a 92-year-old woman diagnosed with Alzheimer disease and cerebrovascular lesions (mixed type Dementia). She was born in Cairo where she lived most of her life working as a reporter, shorthand typist and then as director of the Greek embassy, since she was highly educated and had excellent knowledge of five languages. A. had a wide social circle and due to her noble personality she managed to maintain good public relations with distinguished Greeks of all social levels both in the mainland and abroad. A. has excelled in poetry and was the private secretary to a renowned Nobelist Greek poet for quite a long period of time. She was married to an Italian engineer whom she lived with until his death. In the last fifteen years, the patient has been living with her husband in Athens. During that time, she has suffered mental and physical abuse, and financial exploitation by close family members and social circle that coveted her assets. Up to that point, A. had not been hospitalized or mentioned other medical problems. However, as a result of the intense physical and psychological abuse she had suffered during that time, and following a relative's intervention, she was diagnosed with depression and advanced dementia by her attending physician who has been monitoring the course of her medical condition hitherto. The diagnosis made in 2010 as a mixed Alzheimer's type with atrophy in the hippocampus and ischemic lesions. No other particular problems were reported except for the unattended cataract, and A. was given medication. **Intervention Plan.**The intervention plan includes drug treatment and a physiotherapy program maximizing and strengthening movement potential, by a trained physiotherapist. Furthermore, A. has been integrated into an individual memory training program. On an occupational therapeutic perspective, instructions have been given to adjust her living facilities accordingly so that they are functional to her needs. As a result, all carpets that could complicate walking and contribute to the risk of potential falls have been removed, whilst, safety grab bars and handles have been placed in several parts of the house such as in the bathroom. Finally, A.'s caregiver has been provided with psychological training in order to be able to handle various conditions. **Results.** A. now lives under the care of and in the guardianship of her relative after a court procedure that was followed to appoint her relative as a guardian for her and her assets. After one year of monitoring, A. has exhibited improvement in the MMSE test in which she scored 14/30 upon the first assessment, followed by 16/30 upon a second assessment. Further significant improvement has also been noted in her psychological state and communicational skills. A. continues receiving medical treatment, and physiotherapy treatment from a physiotherapist, while significant attention is given in memory strengthening through daily stimuli. Moreover, the patient's positive psychological state is a significant factor which is mainly achieved due to the intensive care that she receives, in terms of personal hygiene, appearance, medical monitoring and socialization, elements that aim to the improvement of the patient's life quality.

Effects of selected biosynthetic cyclic peptides on Aβ oligomer formation and on the toxic action of Aβ oligomers in primary neurons

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Abstract

An increasing body of evidence supports the hypothesis that soluble oligomeric forms of Aβ are the toxic species in Alzheimer's disease. Many studies suggest that an interaction of Aβ oligomers with the neuronal surface, followed by a cascade of adverse events, leads to neuronal cell death. In the present study, we investigated the possible interference of two selected biosynthetic cyclic peptides (peptide A and B) with: a) in vitro Aβ oligomer formation, b) binding of the Aβ oligomers to the neuronal surface and c) oligomer-induced cytotoxicity, in primary mouse cortical neurons. Aβ40 or Aβ42 peptides were pre-incubated in the absence or presence of either cyclic peptide and the effects on Aβ oligomer formation were assessed by Western blot and dot blot analysis. Results suggest that both cyclic peptides lead to an increase in the amount of low molecular weight oligomers. Also, the effect of either cyclic peptide on Aβ oligomer binding to the neuronal surface and the structural integrity of axons was evaluated by immunofluorescence staining. Our data indicated that the cyclic peptides inhibit binding of Aβ species on the neuronal surface and Aβ-induced neurotoxicity.

Can religiosity levels differ among cognitively intact, MCI and demented elders? Preliminary results

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Abstract

Introduction: The religious life constitutes a significant factor, which is considered to be related with mental status in elders. According to literature (Boyle et al., 2010), religious attitudes can have a protective role in cognitive decline in elders, because it gives the sense of purpose in life. **Aim:** The current study tried to investigate possible associations between religiosity and cognitive deterioration. Specifically, the scope was to find whether the religiosity levels were higher in MCI and cognitive intact elders compared to patients with dementia, highlighting the protective role of religious beliefs in elders. **Method:** Religiosity was measured using the Systems of Belief Inventory (SBI-15R, Holland, et al., 1998), which was standardized in Greek population by Assimakopoulos, et al. (2009). The diagnosis of dementia was set by the neurologist of the day centre of Alzheimer Hellas 'Saint John'. The sample included 345 participants (100 controls, 150 MCI and 95 patients with mild dementia) aged from 55 to 90 years old. The majority of the participants were females (women 69% and men 31%). In order to evaluate our hypothesis, we used the SPSS v 20 and specifically the ANOVA test and Pearson correlation.**Results:** According to the ANOVA test, statistically significant difference regarding the level of religious beliefs was found between normal elders and participants with MCI (p=.014) and normal and demented elders (p=.04). Specifically, elders with MCI had higher levels of religiosity compared to the cognitively intact participants. Nevertheless, no statistically significant differences in terms of religiosity levels were demonstrated between MCI group and patients with dementia (p=.960). Additionally, Pearson correlation showed no significant correlation between depression levels and religiosity levels in the control and MCI group, whereas there was statistically significant relationship between GDS sum score and SBI-15R (sum score (p=.030) & the subscale of Religious beliefs & practices (p=.009). **Discussion:** Taking into account the above outcomes, we conclude that those who had mild memory problems, or have been diagnosed as demented, were more likely to have religious attitudes and participate in religious ceremonies. Moreover, the total score of religiosity levels did not show to be related with depressive symptomatology. However, low depressive symptomatology was correlated to higher levels of religiosity among patients with dementia.

The involvement of bacterial metabolites rhamnolipids in Alzheimer's disease

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Abstract

Alzheimer's disease (AD), the most frequent cause of dementia, brain atrophy and amyloidosis can be caused by chronic bacterial infections. Microorganisms may be contributors in the generation of senile plaques in AD. Many pathogens were reported to be associated with AD including Chlamydophyla pneumonia, Treponemas, Borrelia burgdorferi and the over 200 different spirochetal species or phylotypes of Gram negative as Helicobacter pylori, helical bacteria spirochetes etc. Rhamnolipids (RLs) are glycolipids, bacterial metabolites that are produced by some bacteria mainly by Pseudomonas aeruginosa, and their important role is that are "incriminated" as bacterial virulence factors. Plethora other bacteria except P. aeruginosa found to produce RLs, as Burkholderia, Enterobacter, Escherichia coli, Acinetobacter, Pantoea species etc. In our study RLs were isolated from serum and their existence is identified with various methods. Purified RLs were produced by bacteria and were used for the production of specific antibodies against RLs, which were titrated and evaluated previously. The antibodies against RLs were further used to detect the presence of RLs in sera and cerebrospinal fluid of Alzheimer-infected and controls patients. This study provides evidence for the association of these bacterial secondary metabolites of pathogens with AD.

Commentaries

Items of organisation of space and behavior in it: complexity, transdisciplinarity and synthesis in memory degeneration and urban environments

Mit Mitropoulos

My mother's MCI Memory Degeneration started 7/2007 with a space disorientation crisis. Right from the beginning having become aware of the lack of dependable medical care and cure, we realised the complexity of the brain processes and went non-pharma.We did so by falling back on our background, the family being traditionally ocean-goinbg mariners, myself on networks research,and my mother and I having shared travelling by boats/trains/planes (in that order) as from my age of 6. My mother besides having stayed for years on the side of my father on board, when Captain George left the seas, she was enthusiastic in playing host to a wide variety of friends and splendid visitors to our village summertime home. We have been lucky to have made (as from over 7,5 years ago) the useful hypothesis of potential possible brain-initiated new routes for signals moving from A to B bypassing damaged spots/channels/areas thanks to the very complexity of the brain that has been also defying efforts for pharmaceutical solutions: we pursued physical and brain-soliciattion exercises that became our daily routine. Based on behavioral processes we started with a choice from the Tsantali-Tsolaki collection of exercises (a prof Tsolaki gift), we then went on to personalise them, we later moved on into relational exercises, and now have passed on (as from early 2014) with more visual material--all along making connections with current events so as to feed into newspaper reports and commentary as one easy source of printed information updates.

Good morning, Dementia!
How Alzheimer Cafe became successful in Slovenia

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Slovenia has 2 million inhabitants; there are more than 32 thousand people with dementia in Slovenia, around 9 million people with dementia in Europe and more than 44 million worldwide. According to the forecasts of medical experts, number of people with dementia could triple by 2050. Accordingly, by 2050 around 100.000 people with dementia will live in Slovenia, around 27 million people in Europe and around 130 million worldwide. Dementia is becoming global problem. Are we aware of this?

How many caregivers know how to take proper care of them and how to enable better life both for the patient and, equally important, for themselves? Do they understand what dementia is?

In order to help the caregivers and make dementia more transparent and less stigmatised, professor Dr. Aleš Kogoj, a psychiatrist from the Psychiatric Clinic in Ljubljana, established Spominčica (Forget-me-not) as early as in 1997: – the Slovenian Alzheimer Association. Throughout his life-long experience as a doctor and the president of the Slovenian Alzheimer Association, Dr. Kogoj repeatedly found that dementia did not affect only patients but also their caregivers. The latter, namely, find it difficult to accept the changes caused by the disease. Especially relatives need proper information on difficulties and troubles brought on by dementia. Moreover, the relatives of the people with dementia need full support and concrete assistance how to deal with a person with dementia, while this protracted disease progresses. Why is that so? Although dementia is not a fatal disease, unfortunately there is still no remedy available. On average, dementia lasts ten to fifteen years and patients need a 24-hour loving and affecting support and assistance for many years, since they become incapable of taking care of themselves.

In this respect, the Slovenian Alzheimer Association endeavours to offer as much support to the relatives as possible. The Slovenian Alzheimer Association has established several branches throughout Slovenia performing significant tasks also in local communities. There are more than 16 of them in existence presently.
In order to facilitate the lives of the relatives, the Slovenian Alzheimer Association performs the following activities:
In 2013 we have re-launched our newsletter Spominčica as a supplement to the magazine Naša žena which was published on first of September, the world month of Alzheimer Disease, and distributed in 19,000 copies. The

magazine was already published in 1999 in a limited edition (2,000 copies) and distributed only in hospitals, nursing homes and similar institutions.

Accordingly, Spominčica became accessible to a wider circle of general public, since the magazine Naša žena is one of the leading lifestyle magazines in Slovenia. The newsletter is supposed to be published three to four times per year. Our special emphasis in the newsletter is to raise awareness of dementia and make first signs of dementia recognizable in order to encourage people with dementia or their family members to visit the family doctor as soon as possible.

The first ALZHEIMER Cafe was organised in July 2012 in Fužine nursing home in Ljubljana by the Slovenian Association Spominčica. The first one immediately turned out to be a great success and gathered more than 100 visitors. For the event we prepared a media promotion, one of the most distinguished daily newspapers published an exclusive interview with the President of Spominčica who shared her story of her husband affected with dementia at the age of 50. He was a well-known public personality, a journalist, a dissident and critic under the former system, a human rights' activist, a poet, a translator, a member of the Parliament and a diplomat - the first bilateral Ambassador of the Republic of Slovenia in Belgium, Netherlands and Luxembourg. In 2000 when back in Slovenia he was again elected in the Parliament and it was then that the problem arose, he was not the same person as before; he used to be an intelligent provoker and fighter, and suddenly he was sitting there in silence; the diagnosis was established in 2005.

After the diagnosis it was unclear when the symptoms of Alzheimer disease arose. They were not recognized either at home or in Parliament. Today I know how significant it is to recognise the first signs of disease and how important it is to get an early diagnosis. I was aware that something was wrong with him but I hoped that problems were temporary. With the diagnosis there is no more hope! After the diagnosis a new life starts, and this new life is a life of doom. Information, support and incentive can make life of a patient with dementia and his caregiver more bearable. When I think it over, it was the years before the diagnosis that were the hardest of all, sensing the changes in character, secretly watching the decay of functions, trying to bring out his former abilities and suffering when all was in vain. After the diagnosis I calmed down, accepted the inevitable and did everything to improve my husband's life or at least to make life bearable for both of us. I started working with Alzheimer Europe in Alzheimer Slovenia to help and share what I experienced with those afflicted with the same disease and forced to suffer the same fate.˝

ALZHEIMER CAFE is an activity that we launched in July 2012. We became acquainted with these cafes at one of the meetings of the Alzheimer Europe in Brussels. The Alzheimer cafe idea originated in Holland when in 1997 Dr. B. Meisen realized that help has to be extended to family members as well. He organized the first meetings which spread fast across the country and soon to other European countries. At these gatherings, a special emphasis was placed on the relatives who find themselves in a difficult situation not knowing how to deal with patients. Such gatherings take place in public cafes, libraries, shopping malls, city squares and elderly people's home and attract a great number of participants. Such awareness raising gatherings that take place outside the medical institutions and assist with destigmatisation of dementia, are likewise supported by the Alzheimer Europe. It is of great importance that the relatives of patients have an opportunity to meet, exchange their experiences and mutually help each other. In addition, the relatives have an opportunity to discuss the difficulties they are facing in dealing with dementia patients with experts at Alzheimer cafes.

One of the main tasks of Spominčica is to raise public awareness, to help with recognition of the first signs and to help to destigmatize dementia.

Why did Alzheimer cafes spread so fast across Slovenia? Because we advertise them in national newspapers, local newspapers, on radio, our website, on Facebook, on Twitter, in nursing homes. We have a well-established network of local units, which have already been active for a long time. The Ljubljana Office is the coordinator that helps to find lecturers and provides all the necessary information.

Summary: It is clear that there was a great need for this informal type of gatherings, where in a relaxed atmosphere in the presence of an expert and volunteers from Spominčica they can meet each other and exchange experiences and information. Just a conversation with people who understand you counts a lot.

Halo effect: we have to emphasize that the reach of Alzheimer café is much greater than just including the participants, because with advertising we reach the general public, raise public awareness and help to destigmatize dementia.

Over the past year there were more than 40 Alzheimer Cafes in different places across Slovenia, also in some smaller cities such as Komen (500 inhabitants, they regularly organise AC in the library).

Our SOS phone line 059 305 555 provides assistance three times a week (Mon, Wed and Thu from 12 a.m. to 3 p.m.)

Additionally, we invite our clients also to individual discussions and consultations when necessary. Our association Spominčica welcomes clients to individual discussions every day from 10 a.m. to 2 p.m.. Our telephone in the office is 01 25 65 111.

Occasionally our association also publishes awareness raising and informative leaflets. Within the framework of our programme »Don't forget me« we also organise trainings for relatives. The programme consists of 8 lectures. Furthermore, we organise trainings for SOS staff and medical staff who work at homes for the elderly.

We are planning to organise trainings for medical staff working with dementia patients, volunteers, public workers who are in constant contacts with the patients (police, bank clerks, salespersons, etc.). These trainings are considered to be a part of the project Dementia friendly environment which is recommended and supported by the

Alzheimer Europe. In addition we are also planning to organise nursing care at home. Namely, a demand for nursing home care increases rapidly.

In September the World Alzheimer's month we organise several events, roundtables, press conferences etc. every year. The journalists are invited on a regular basis, there are many articles in newspaper, and we are invited to TV and Radio. These awareness raising events culminate on 21 September when we organise a Memory walk under umbrella of Mayor of Ljubljana, the capital of Slovenia in the centre of Ljubljana. Memory Walk is organised on the same day in other towns throughout Slovenia, commemorating the World Alzheimer day. In fact, this action is organised throughout the world upon the recommendation of the Alzheimer Disease International with headquarters in London. By the way: the Slovenian Alzheimer Association joined the organisation in May this year.

Our association Spominčica holds its website: www.spomincica.si, and is active also on the social media: Facebook in Twitter.

Daycare centres: in Slovenia we avail of a growing number of daycare centres that are well organised and patients-friendly. We are cooperating with several NGOs and are included into inter-generation programme supported by Government. Solidarity and mutual help within population in Slovenia is traditionally well developed and families with dementia patients enjoy a sound support by a number of various organisations. Nursing the patients is well organised; on the other hand, however, we have not developed a well organised nursing care network at home as yet.

We believe that Slovenia is officially not aware of the problem of dementia yet, since our country has not yet accepted the National Dementia Plan. The Slovenian Ministry of Health established, at the initiative of a few people from the Alzheimer Slovenia in 2010, the first Working Group for preparing the National Dementia Plan; the Report has been elaborated as a draft for a national plan. In 2013, the second Working Group with 10 representatives has been established, while some of us come from the Alzheimer Slovenia. WE believe that Slovenia will soon produce this document. We should not forget that dementia is one of the most expensive diseases. Namely, it is a protracted disease (on average it lasts 10 to 15 years) and the patients depend on their relatives, medical and other experts since they need 24-hours' assistance. They often prove dangerous to themselves as well to their social environment.

Last but not least: The heart and the engine of our Association are our volunteers. If we want to fulfil all our obligations and needs that are increasing every day, we would certainly need more support and understanding at the national level. The majority of states have already launched dementia to the principal public health priorities. We certainly hope and believe that Slovenia will follow this practice very soon.

Next generation sequencing technologies for whole exome/genome sequencing: impact on daily clinical practice, in dementia and beyond

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The diagnostic advantages and the challenges encountered using NGS in the clinic: presentation of selected cases

The human genome is composed of 3 billion DNA bases, of which approximately 1% (30 million bases, distributed in the about 20,000 functional human genes) are coding for proteins. Compared to the arbitrary human reference genome, variations in these coding sequences account for the benign polymorphic features that make each human being unique. On the other hand, it is estimated that up to 85% of the disease-causing or disease-associated variants reside also in these coding gene regions, termed exons. Therefore, sequencing of all the exons of an individual (termed Whole Exome Sequencing-WES) is associated with a high probability of identifying a disease-causing mutation for a Mendelian disorder or a disease-associated variant for a complex disorder. This has been recently made possible at an affordable cost with the use of next-generation sequencing (NGS) technologies. As a consequence, WES is increasingly adopted in everyday clinical diagnostics, and it is changing the way medicine, and neurology in particular, are practiced.

Indeed, several studies so far, as well as our own experience with WES in more than 50 patients, have shown that the diagnostic yield of WES is high (ranging from 25 to 40%), especially when aiming to detect the genetic cause of diseases characterized by locus heterogeneity and overlapping or non-specific symptoms (e.g. neurodevelopmental disorders). This translates to substantial patient benefit at multiple levels, including disease treatment and complications management, family planning and earlier (even pre-symptomatic) diagnosis in other family members.

At present, there are several limitation to WES, depending on the way it is performed. These limitations include incomplete coverage of the exome, variable accuracy and lack of standardized protocols for pathogenic variant filtering, identification and annotation. However, even in the case of patients that definite diagnosis is not achieved at present, the ability to store indefinitely their raw data, along with the continuous enrichment of public databases, is expected to allow disease variant identification in the future by a simple re-analysis of the existing WES data. Moreover, data sharing for the purpose of evaluating pathogenicity of clinically relevant genomic variants enables genome data interpretation in a variety of clinical contexts. Furthermore, WES technologies have been instrumental in genetic research, by allowing the identification of, thus far eluding detection, genetic variants tied to diverse phenotypes.

This overwhelming technology is not free from several ethical issues, which are associated with the safety and anonymity of the genetic data, the report of the relevant to the current phenotype genetic findings and the report of the so-called incidental findings. It goes without saying that genetic data for each individual tested should be used only as his/her informed consent document dictates and should be safely and anonymously stored. Also, relevant genetic findings should be communicated in the context of an appropriate genetic counseling. Finally, incidental findings of clinical importance (present in about 2-3% of patients undergoing WES) should be actively sought and reported to the attending physician of the patient. These incidental (or secondary) findings are not related to the indication for ordering the NGS analysis, but may nonetheless be of great value to the ordering physician and the patient. Even though the American College of Medical Genetics and Genomics has recently published recommendations on the reporting of incidental findings, there is an active debate regarding the utility and ethics of returning these results to patients based on the possible effect these findings might have on patient's quality of life and the commitment of his future. In this respect, for example, there is growing discussion on the clinical value of incidental pharmacogenomic findings in unselected populations.

Thus, several challenges are encountered when implementing NGS in daily clinical practice. Critical questions that often arise are:

- What are the advantages and limitations of NGS testing?
- How to obtain informed consent from the patient or his/her legal guardian?
- What types of tests should be ordered?
- How and what results should be reported?
- What interpretative support is required immediately and over time?

To answer these questions, this session on NGS technologies and their application for clinical WES (or even, in the near future, Whole Genome Sequencing-WGS) will review recent progress in the incorporation of these technologies in the daily clinical practice of physicians caring for patients with neurodegenerative and other neurogenetic diseases. To this aim, we will present cases where WES has proved successful for us, illustrating the value of exome sequencing as an efficient diagnostic tool for complex neurodegenerative disorders. In specific, evidence will be presented on the clinical value and the challenges encountered using WES in patients with various forms of dementia.

In our hands, as in those of others, these NGS-based molecular diagnostics have been remarkably effective in solving the diagnostic riddle in several patients with suspected Mendelian genetic disorders. Many of these patients had remained undiagnosed and at risk for inappropriate, costly therapies, with significant negative impact on their quality of life. In this session, we will provide insights into how the high diagnostic yield and cost effectiveness of WES ended the diagnostic odyssey of these patients with neurodevelopmental diseases and neurological disorders of variable genetic etiology, including dementive disorders.

In addition to discussing the contribution of molecular diagnostics to the care of patients at the present time, and anticipated progress in the near future, this session will also address the issue of how NGS should be standardized and appropriately integrated into professional medical practice. We will also discuss the need for returning secondary results to the ordering physician, who will thus be in a privileged position to integrate these secondary findings with the clinical phenotype and the family history, allowing their interpretation in an appropriate clinical context.

To serve this aims, we have established a program at the University of Crete that allows neurologists and other physicians, from Crete or other parts of Greece, to perform WES (or in the future WGS) for their patients in a standardized way and receive clinically relevant results in a timely manner. This program, among others, offers support to the ordering clinician on how to order the test and obtain inform consent, and also allows interaction on the clinical interpretation of the WES data.

Concerning research purposes, we are in the process of implementing WES technologies in search for causative variants in families with late-onset Alzheimer's disease (or other neurogenetic disorders) apparently inherited in a Mendelian fashion. These families are identified either through a program funded by the European Union and Greek national funds (THALES: UOC-Multidisciplinary network for the study of Alzheimer's Disease, Grant Code: MIS 377299) or through collaborating researchers.

As the cost of NGS (both WES and WGS) is continuously dropping (with the cost of WES currently being less than 1000 euros per sample, but expected to lower more in the near future), more and more clinicians, including neurologists caring for patients with dementia, will be confronted with the need to order these tests and interpret the results of such testing in the appropriate clinical context. As such, familiarity with the indications, procedures and limitations of NGS (WES or WGS) technologies is increasingly needed.