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Exploring modeling analogies between living and non-living systems

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Abstract

This paper aims at illustrating how both living and non-living systems can be modeled and examined in similar ways. After a brief discussion on the use of similar types of differential equations that can be employed for the description of spatio-temporal patterns in deforming solids on one hand, and the description of cell evolution in brain tissue on the other hand, we focus on situations for which equations are not available or possible to derive for modeling system behavior and corresponding experimental data. The experimental data we are referring to concern signals and images for which deterministic methods cannot be applied to interpret the observations. Thus, we first provide an account of what signals are, and how they can be analyzed. We then proceed to elaborate on specific methods (fractal analysis and informational analysis) that have yielded encouraging results, underlining how the analysis is identical in both living and non-living systems. Lastly, specific results are presented and analyzed.

Keywords: Living systems - Non living systems - Modeling analogies

Introduction

It is a common trend to use methods and tech-niques developed in physical, chemical and engineering disciplines to interpret phenomena in biology and medicine. The fields of biophysics and biomechanics have emerged as a result of this trend. A most no-table example is the seminal reaction-diffusion model of Turing, equally applied to describe pattern formation in chemical systems, and to spatio-temporal evolution in living cells. The idea was essentially adopted by Nobel Laureate Prigogine to determine self-organization in a variety of \far from thermo-dynamic equilibrium" living and non-living systems. Along more specific lines, Aifantis [1, 2] introduced the effect of an externally applied stress as being the driving force for pattern formation of defects in metals. At the same time Murray [3] introduced the effect of internal stress developed during the “crowding” of cells in the extracellular matrix as being the driving force of morphogenesis in living tissue. Coupling phenomena

between motion/production of dis-location defects in solids or motility/proliferation of cells in tissue are accounted for by the Laplacians of strain modeling diffusion and Laplacians of strain modeling nonlocal effects between the moving species and the accommodating surrounding metal or tissue matrix. The corresponding “diffusion coefficients’ multiplying the Laplacians of the concentrations of the di using populations and the “internal lengths” multiplying the Laplacian of strain are treated as phenomenological parameters to be determined by microscopic modeling and simulations with input from related experiments. A recent comprehensive review on the internal length gradient (ILG) mechanics approach and its applications to modeling a variety of materials and processes across scales and disciplines can be found in [4].

A special case of the ILG approach is the so-called Walgraed-Aifantis (W-A) model [5{8] for dislocation patterning in metals under applied cyclic stress. The W-A model is a set of two R-D equations for immobile and mobile dislocations which organize themselves in periodic layered structures (persistent slip bands / PSBs) under the action of external stress. It is remarkable that similar type of equations were independently proposed for cancer. The corresponding set of R-D equations is commonly referred to as the Go or Grow (GoG) model. The “mobile” dislocations correspond to “motile” cells and the “immobile” dislocations correspond to “immotile” cells. An extension of the W-A model was proposed in a yet-unpublished work by Romanov and Aifantis, which describes the spatio-temporal evolution of defects in nanomaterials produced by repeated severe plastic deformation (SPD). There are 4 types of structural defects in this case: Immobile intragranular dislocations, mobile in tragranular dislocations, grain boundary dislocations, and disclinations in triple-grain boundary junctions. The R-A model was recently shown (also in unpublished work) to be able to describe the interaction of cell populations during the progress of Alzheimer's Disease (AD). The relevant biological populations here are identified with microglia, astroglia, neurons, and Ad amyloid.

Results on stability analysis and numerical solutions of the above type of deterministic R-D equations for non-living nanomaterials and living brain tissue are in progress and will hopefully be reported in the future. The focus of the present note, however, is on situations where deterministic differential equations are not possible to derive for describing complex aspects of system behavior captured by modern experimental methods based on signal analysis and image processing. For example, high-resolution microtensile devices can now capture signals of serrated stress-strain curves reflecting the effect of stochastic evolution of the underlying micro/nanostructures. Similarly, advanced electroencephalography (EEG) captures signals that need to be analyzed with fast algorithms for revealing universal statistical features. The same holds for images obtained through optical, electron and atomic force microscopy or magnetic resonance imaging and positron emission tomography. Again efficient algorithms need to be employed for analyzing the details of such images and measure corresponding statistical indices such as fractality and lacunarity. An exploration on the use of such types of signal and image analyzes for complex features of systems that cannot be described by deterministic models is attempted herein.

Signals and Signal Analysis

Scientific progress is evolving by gathering information. This information is everywhere around us: It

is in the vibrations of the ground, it is in the temperature of the air, it is in the mannerisms of ourselves and the people around is. Those things, those that contain useful information inside them, are called signals.

Signals can be a surprisingly deep source of information. For instance, a human that hears a simple “hello” can derive information on who is speaking, their emotional state, if they have a study nose and so on. When we study a signal in order to extract the information hidden inside it, this is called signal analysis. Some of it can be done by humans, obviously, but a large amount of information is hidden to us. To decode it, we enlist the help of computers.

Signals vary immensely in their form, so speaking about them in general terms can be di cult. Perhaps the most fundamental way that they can be categorized is the amount of independent and dependent variables that they have. For instance, an audio signal has time (1 independent variable) and intensity (1 dependent variable). A grey-scale image has height and width (2 independent variable) and luminosity (1 dependent variable). A Magnetic Resonance Image (MRI) has 3+1, and a color image has 2+3. Due to this variance, it is a great advantage for a method of analysis to be equally applicable in every kind of signal regardless of dimension. Because the aim of this paper is to introduce similarities between analyzing methods of different scientific disciplines, we have therefore elected to introduce methods that are applicable regardless of the total amount of dimensions.

There has been a plethora of such methods, each with its strengths and its weaknesses, that has been developed since the development of information theory. Here is a minuscule sample:

Fourier analysis decomposes a signal into the frequencies it is composed of. In a musical piece, this would be equivalent to “decomposing” it in order to find the original musical score. Of course, Fourier analysis has many more applications.

Stochastic analysis describes the values that a signal tends to oscillate around, and how wide the oscillation is. It treats every sample we have as an unordered part of a whole, without consideration to the order in which they appear.

Informational analysis describes the predictability of our signal. In contrast to statistical analysis, it does not examine values individually, but examines the probability of each value given the ones that came before it. In layman's terms, it describes how likely we are to learn something new with each successive sample.

Fractal analysis describes the roughness or smoothness of our signal, as well as its homogeneity or in-homogeneity. It is particularly applicable when examining what has changed in the structure of a signal.

The gamut of fields that can benefit from signal analysis is as broad as science itself. For instance, in seismology we can differentiate between the different types of seismic waves that came, in economics we can predict market trends, in material mechanics we can predict a material's toughness, and in biomedicine we can estimate the health of an individual.

Before we begin explaining further, there is an important point that needs to be made: Due to space constraints, the explanations of the metrics and methods discussed in this paper are delivered in a sketchy way and with some vagueness. For a deeper understanding of them, we urge the reader to refer to specialized literature.

Fractal Analysis

For a very broad and rather vague understanding of Fractal Analysis (henceforth FA) it would suffice to think of it is a method to quantify how “rough” or “smooth” a given shape is. However, we judge it prudent here to spend some time explaining it further, in order to fully understand its significance in the diverse fields that we study.

In essence, fractal geometry aims at covering the gaps presented by ordinary Euclidean geometry. It began with the realization that there are several shapes (made both by human and by nature) that stubbornly resist description by ordinary Euclidean geometry. Clouds, mountains, coastlines alike have shapes that do not resemble any well-known Euclidean shape, as they seem to unveil new detail every time we attempt to look at them more closely.

The quintessential example of a fractal shape is one that can be described as a collection of smaller sub-shapes, every one of them similar to each other and to the original shape. Such shapes belong mainly to the domain of mathematics, as nature tends to insert randomness that drives shapes away from full self-similarity.

There are innumerable categories of fractal shapes. Here, we would like to explain two: Dendrites and Tremas.

Dendrites are structures that contains an original line, from which branches (bifurcations) begin protruding. After that, each new line created that way is bifurcated further, and so on recursively until every line in the shape, to the extent that we can see, bifurcates at some point. A few examples of dendrites can be found in Figure 1.

Tremas are structures wherein a specific shape has been continually removed, in various sizes, from every part it could. Examples of tremas can be found in Figure 2.

These examples have been chosen specifically to highlight the close similarities that can be found between organic systems, non-organic systems, and computer-generated systems. Each of these shapes looks distinctly like the others, despite the great differences in how they were created.

Informational Analysis

The word “entropy” has several different meanings that seem really disparate at first glance. It was first introduced through the field of thermodynamics. In that field, it can describe several notions, one seemingly unrelated with the other. For instance, it can describe the seeming irreversibility of a given phenomenon, such as an explosive that can be ignited, but never de-ignited. It can alternatively quantify how dispersed or concentrated the differences in temperature are, as in the example of a glass with ice cubes that have not yet melted. Of course, it makes no sense to talk about the temperature of a signal; we therefore use the alternative explanation of entropy, i.e. disorder, and its surprisingly close relative, information.

As an example of order or disorder, let us imagine a jigsaw puzzle. Every one of its pieces can, at any point, be at any place on the table. (Regardless, for simplification purposes, we will assume that the position and orientation of the top left corner is fixed.) When the puzzle is complete, it is in a sense fully ordered. In contrast to that, when each piece is in a random place on the table, then the puzzle is completely disordered. The things to notice about this are two:

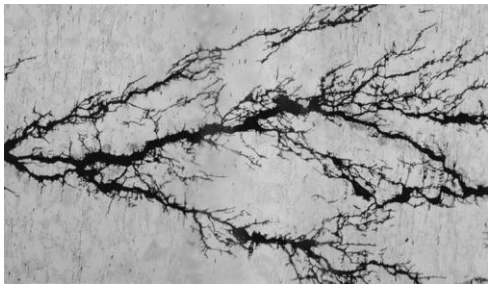
- There is only one way that the puzzle can be considered to be solved. In contrast, there are

infinite ways that the pieces could be randomly spread on the table; each of them distinct from one another, yet all of them falling under the label of “completely random”.

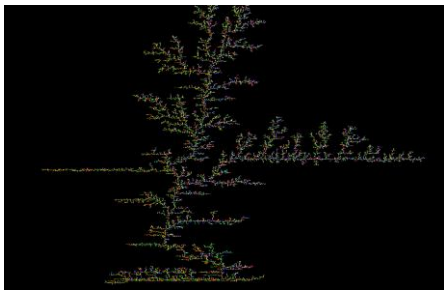
- When a puzzle is solved, the mere assertion that it is solved is enough to fully describe the position and orientation of each piece: in other words, it can be described using very little information. In contrast, when every piece is placed randomly, one would need to describe every piece individually, i.e. it would require lots of information.

With those things in mind, we can begin to see that a) disorder and information are strongly linked and b) that both can be quantified by examining the probability of finding our system in some situation (state) vs another. In general, the definition of the entropy of a specific situation is $S(p_i) \propto p_i \log p_i$,

a) An example of dendritic structure in neurons

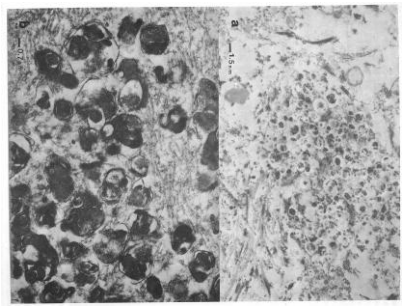


b) An example of dendritic structure in faults of steel.

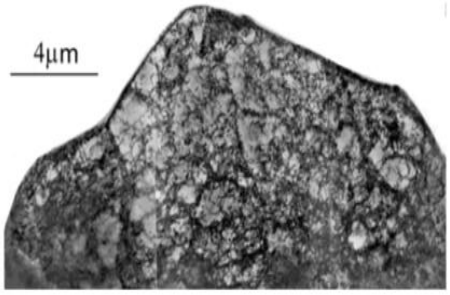


c) A computer-simulated dendrite.

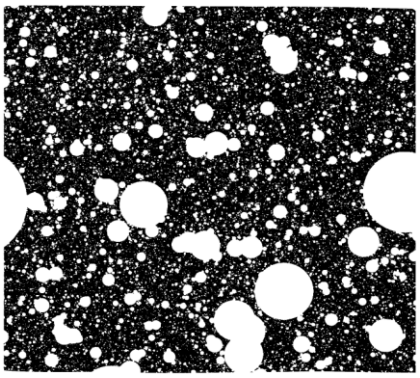
Figure 1. Dendritic structures in living and non-living systems.



a) An Alzheimer's Disease related plaque in the brain



b) A plaque of table salt, cracked under high pressure.



c) A computer-simulated plaque ("trema").

Figure 2. Fractally-shaped plaques in living and non-living systems.

and the total entropy is the sum of all of them, i.e.

$$S \propto \sum_{i=1}^{n} p_i \, log p_i \qquad (1)$$

The definition we have given is called the Boltzmann-Gibbs entropy. We can see that, because the total entropy is equal to the sum of each partial entropy, this definition is additive. However Tsallis, in [9], posited that this is not necessarily true for all cases, especially when the system is driven far away from thermodynamic equilibrium, often approaching chaotic regimes. He offered an alternative definition of entropy, dependent on a parametre q to be derived empirically for each specific case, defined as

$$S(q) \propto \frac{1}{1-q} \sum_{i=1}^{n} p_i^q \qquad (2)$$

t turns out that when q → 1, Tsallis entropy reduces to the Boltzmann-Gibbs entropy mentioned above. In [4] Tsallis formulation is briefly reviewed and it is shown that his nonextensive entropy q-statistics can describe serrated stress-strain curves of nanomaterials, and also provides fractal dimensions of corresponding deformation patterns obtained through scanning electron microscopy (SEM). In [10] Tsallis q-statistics were used to analyze electroencephalograms (EEGs) from patients suffering from neurodegenerative disorders. In the next section we present some preliminary results of using fractal algorithms to deduce the fractal dimension and lacunarity that can potentially be used as biomarkers for disease diagnosis.

Preliminary Results

Part of the reason that we chose those specific methods of analysis is because our laboratory has made recent important progress in the development of methods to compute them. A few preliminary results can be found here:

- With regards to fractal dimension analysis, we conducted a preliminary test on a set containing 16 Magnetic Resonance Images, 11 of which depicted patients with Alzheimer's disease and 5 of which depicted healthy patients. It was found that D = 3:32 seemed to be a good limit between sufferers and non-sufferers, as 4 healthy patients had an MRI whose FD was higher, and 8 patients had an MRI whose FD was lower.
- With regards to lacunarity analysis, a set of 16 couples of images was examined. Each couple contained a picture of cancerous tissue and a picture of neighboring healthy tissue. In 93% of the cases, pictures which depicted cancerous tissue had a lacunarity lower than 6, whereas pictures which depicted healthy tissue had a lacunarity higher than 10.

Conclusions

Our aim was to illustrate the similarities between mathematical models developed for describing morphogenesis in nonliving novel nanomaterials and pathogenesis in living brain tissue under the action of external or internal stress. More importantly, it was shown that such type of analogies between the phenomenology of living and nonliving systems can go deeper with respect to common methods used for analyzing statistical features of signals and images obtained by advanced tools of modern technology, not captured by deterministic phenomenological models.

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All authors declare that they have no conflicts of interest.

Sources of subfigures:
1a, 2a: Courtesy of prof. Stavros Baloyiannis.
1b: [11]
1c: Wikimedia, ©CC BY-SA 3.0.
2b: [12]
2c: [13]

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Metacognition in MCI: a research proposal on assessing the efficacy of a metacognitive intervention

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Abstract

Introduction: Mild Cognitive Impairment (MCI) is the transitional phase of cognitive deterioration between healthy aging and dementia and has considerably attracted the scientific interest. Numerous studies have explored the cognitive functions (CF) and their decline in MCI, whereas very little is known about the metacognitive functions (MF) at this stage. Aim: The aim of the proposed thesis is twofold. First, there is the aim to examine the relationship among MF, CF, and theory of mind (ToM), in MCI patients compared to cognitively healthy controls. Second, it aims to apply and to test the efficacy of a metacognitive training program in MCI patients. **Method**: For the purpose of this study, 150 participants will be recruited and then divided into three groups: a) patients with amnestic MCI (aMCI, n = 50), b) patients with non – amnestic MCI (naMCI, n = 50) and c) cognitively healthy controls (cHC, n = 50). All participants will be tested and compared for the level of their CF, MF and ToM abilities, and potential differences of the prototypes of the relationships among the three psychological dimensions for the three groups will be examined (1st part). The 2nd part of the study is to test the potential effectiveness of a metacognitive training program as regards the enhancement of cognitive, metacognitive, and social cognitive functions in MCI. To do so, the MCI patients will be randomly divided into an experimental and a control group each of which will have 50 participants (25 aMCI and 25 naMCI patients, respectively). Measures of CF, MF, ToM as well as neurophysiological recordings will be taken at four different time points, before and right after the intervention and then again six and twelve months after the intervention. **Conclusion**: The early diagnosis of MCI and the design of metacognitive therapeutic interventions targeting the generalization and maintenance of their results still remain a challenge for the scientists and the health professionals. Thus, the study aims to shed some light onto this gap in research.

Keywords: Metacognition – Mild cognitive impairment – Theory of Mind – Functional connectivity

Introduction

The term Mild Cognitive Impairment (MCI) refers to the intermediate stage of cognitive decline between healthy aging and dementia [1]. It is characterized by cognitive decline, that is greater than expected for age but it does not impair the person's ability to independently function in daily life [2]. MCI is divided into two clinical subgroups, amnestic MCI (aMCI) and non – amnestic MCI (naMCI), depending on whether or not the symptoms are predominant in the cognitive domain of memory [3].

A further distinction can be made on whether the cognitive deficits appear on a single cognitive domain or on multiple domains [3]. Besides deficits in the main cognitive domains, according to a recent study, people with MCI present deficits in theory of mind (ToM) [4]. Longitudinal studies have reported that the transition to Alzheimer's disease (AD) affects approximately 10 – 15% of those who have been diagnosed with MCI [5]. Therefore, early diagnosis of MCI, as well as effective interventions, is of essential importance as they could significantly contribute to delaying the onset of AD or other sub - types of dementia [6].

Recent studies have shown that neuro-pathological aging affects not only the main cognitive functions (CF) and aspects of ToM but it also affects the metacognitive functions (MF) of people with MCI [7, 8]. MF or metacognition refers to a person's awareness about their CF and plays a significant role in the monitoring and regulation of cognitive behavior [9, 10]. More specifically, patients with MCI tend to make less accurate estimations about their CF compared to healthy controls [11, 12]. Furthermore, according to a recent meta-analysis, although patients with MCI are able to make quite accurate estimations about their own cognitive deficits, the degree of their awareness depends on their cognitive resource [13]. Nonetheless, further research is necessary to better understand the role of MF in MCI.

The importance of studying the role of MF is based on their interaction with CF, as well as on the fact that deficits in awareness of one's cognitive state can negatively affect the efficacy of therapeutic interventions [14]. In addition, previous studies have shown that the enhancement of MF not only improves the ability to learn cognitive strategies but it can also result in the transfer of cognitive strategies beyond the context in which they were learned [13, 15-17].

Several studies have provided evidence that interventions focusing on metacognitive enhancement in older adults can significantly promote learning skills [16, 18]. More specifically, the researchers of a recent study compared the results of a cognitive and a metacognitive training [16]. As expected, both trainings helped participants to learn cognitive strategies. However, only the participants of the metacognitive training, which was based on self – testing, showed transfer effects, meaning that they were able to apply the cognitive strategies they had learned to different contexts. In addition, another recent study found that just by discussing how to use already taught cognitive strategies in different contexts can lead to transfer effects [19]. Although metacognitive training seems to have promising results, research is still in its infancy and the available data are mainly referred to the community - dwelling older adult population and not to cognitively declined patients.

Mild Cognitive Impairment and functional connectivity (FC)

The scientific community has considerably benefitted from the development of modern neuroimaging techniques by gaining deeper insight into the neural correlates of many neurological and psychiatric disorders. Due to the heterogeneity of MCI, neuroimaging methods have been proven as a valuable tool in clinical practice [2, 20].

Electroencephalograph (EEG) is a popular neuroimaging method since it is a non – invasive way for recording brain activity. It is well used in research for estimating functional connectivity (FC) of the brain networks, in order to further investigate the brain's organization and functions [21]. Graph theory is widely used for calculating FC, and it suggests that two topographic features are necessary in order to extract the topographic properties of a network and these are: a) clustering coefficient, which refers to the degree to which nodes of a graph tends to cluster together, and b) path length,

which refers to the distance between two nodes of a network [22].

Several studies have demonstrated reduced FC in both MCI and AD patients [21, 23, 24]. Using resting state EEG (rs – EEG), researchers have found a lower degree in the clustering coefficient in patients with MCI and AD compared to healthy controls [25]. Furthermore, scientific data have revealed that patients with MCI show a pattern of brain organization that resembles a continuum between healthy aging and AD [26]. In addition, rs – EEG has been used to estimate differences in FC in MCI patients as a result of cognitive training and it was reported that cognitive training can increase FC [27, 28]. Based on these data, the present study aims to use rs – EEG to investigate FC in MCI and whether it could be altered as a result of a metacognitive training.

Aims and Hypotheses

The first aim of this study is to assess MF and their relationship with cognitive control and ToM, comparing patients with two sub - types of MCI and cognitively healthy participants. Based on this aim, the following hypotheses are formulated:

1. It is expected that aMCI and naMCI patients will show reduced awareness regarding their cognitive skills, compared to cognitively healthy participants.
2. Due to changes at the level of MF, CF, and ToM, it is expected that the pattern of their relationships will be different among the three groups.

The second aim of this study is to apply and evaluate a metacognitive training in MCI patients. The metacognitive training will be compared to a 'traditional' cognitive training. Therefore, the following hypotheses are formulated:

3. (a) The MCI patients who will participate in the metacognitive training intervention will show improvements in MF, CF, ToM and daily functioning after the training is completed. (b) It is expected that these improvements will remain over time. (c) The MCI patients who will follow the cognitive training intervention will show improvements in CF, though to a lesser extent than those of the metacognitive training and it is not expected for these improvements to remain over time.
4. As for the MCI sub – groups, it is expected that both aMCI and naMCI patients will equally benefit from the metacognitive training because it is not a domain specific training but it rather targets to improve the general cognitive state. However, due to lack of scientific evidence, we cannot formulate a straight hypothesis.

To further test the efficacy of the suggested metacognitive training, we will also look for any potential changes in brain organization, using rs – EEG before, right after the training and then again six and twelve months after the training.

5. It is expected that metacognitive training will affect brain organization by enhancing FC of the brain networks. However, due to lack of scientific data regarding the relationship between metacognition and FC, we cannot propose a more specific hypothesis.

Method

Participants

The total sample size will consist of 150 participants divided into three groups matched in age, gender, and educational level: a) patients with aMCI (n = 50), b) patients with naMCI (n = 50) and c)

cognitively healthy controls (n = 50). Participants will be recruited from the Day Centres of the Greek Association of Alzheimer's Disease and Related Disorders. All participants will undergo a neurological and neuropsychological examination, in order to evaluate their cognitive state. The diagnosis of MCI will be based on Petersen's criteria [29]. The age rage will be between 65 to 85 years old. Education status will be at least six years and all participants will be native Greek speakers.

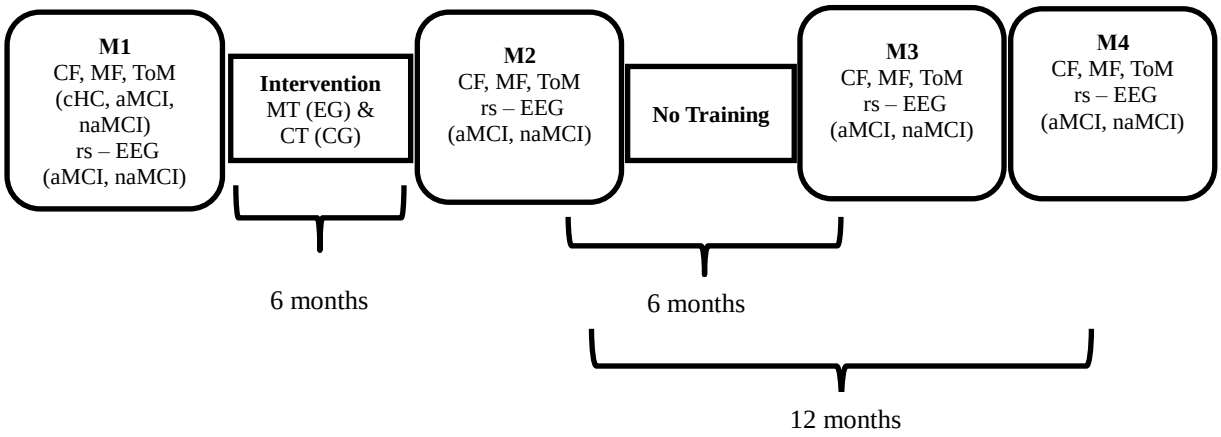
Exclusion criteria will be: past or present diagnosis of neurological disorders, head trauma, psychiatric disorders, and substance – related disorders, smoking, and use of memantine or cholinesterase receptors (the last one only refers to the MCI groups). Furthermore, regarding the group of cognitively healthy controls, they should not present risk factors for dementia and/or cognitive decline. All participants will be given written informed consent prior to participation. Finally, the study will be approved by the local ethics committee.

Design

The design of the proposed study is mixed i.e. cross – sectional and longitudinal. It consists of a cross – sectional study and a randomized study of a personalized non - pharmacological intervention.

All participants will take part in the first assessment (baseline, M1). Afterwards, all participants who have been diagnosed with MCI will be randomly divided into two groups, the experimental and the control group. Each group will consist of 50 patients (25 aMCI and 25 naMCI). The experimental group will receive the metacognitive training, whereas the control group will receive a cognitive training. The training will last for six months and at the end, a second assessment will take place (M2). Then, no training will be received and two follow – up assessments will take place, six (M3) and twelve months (M4) after the end of the intervention. Each assessment will contain tests for the evaluation of CF, MF, and ToM and the neurophysiological recordings using rs – EEG. The cognitively healthy controls will participate only in the first assessment for the estimation of CF, MF, and ToM. Only the MCI patients will participate in the rs – EEG sessions (see, Figure 1).

Figure 1.



Note. cHC = Cognitively Healthy Controls, MT = Metacognitive Training, EG = Experimental Group, CT = Cognitive Training, CG = Control Group

Procedure

During the initial stage of the study, the first step is to inform the participants as well as their caregivers about the procedure. Then, all participants will undergo the first assessment to evaluate their CF, MF, and ToM. The assessment will be divided into two sessions each of which will last approximately two hours and the time interval between the two sessions shall not exceed 7 days. A third meeting will be arranged with each participant (of the MCI groups) to conduct the neurophysiological recordings. All meetings will take place during the morning hours and they will be arranged in consultation with the participants. The same procedure will be repeated for the next measurements (M2, M3, and M4).

The training for both experimental and control group will last six months. We decided to follow the training schedule of a previous study, according to which six months seemed to be sufficient amount of time for promoting cognitive enhancement and transfer effects in patients with MCI [30]. It will consist of individual training sessions, once per week and each session will last one and a half hour. Between sessions, participants will be provided with some homework to do. It should be noticed that the tasks that will be given during the training will be different from those that will be used for the evaluation of the CF, MF, and ToM.

Tools

Assessment of cognitive functions (CF). All participants will receive the same tests and questionnaires, the order of which will be alternated. A number of valid and reliable scales and self – report questionnaires will be used to estimate the general cognitive status and daily functioning. In addition, a number of neuropsychological tests will be administered to assess specifically memory (episodic, working, and prospective memory), executive functions (inhibition, switching, updating, planning), and ToM (the ability to understand metaphorical speech, faux pas commitment, beliefs and intentions of the other).

Assessment of metacognitive functions (MF). To assess metacognition, the Brief Metacognition Questionnaire for the Elderly (BMQE) [12] will be administered, which will be adapted to Greek and tested for its validity and reliability prior to the assessment of MF. A new self – report scale will be constructed to test the efficacy of the participants' CF in daily life and the degree of their cognitive control upon them. Furthermore, a metacognitive version of neuropsychological tasks for memory and executive functions will be administered to assess online processes of metacognition, by adding two metacognitive questions [31]. The first question estimates the degree of confidence the participants have regarding the correctness of their answer. Therefore, after each response, the participant will have to answer the question: "What is your degree of confidence in this answer?" [31, p. 549]. In the present study, we will use a 4 – point Likert scale to estimate the degree of confidence: 1 = not at all, 2 = slightly, 3 = moderately, 4 = completely. The actual performance of participants in each question or cognitive task will be combined with the degree of confidence they give for the correctness of their answers to calculate the accuracy of metacognitive monitoring, and the degree to which they overestimate or underestimate their performance. The second question, "Would you like your response to be included in the total score?" examines cognitive control and to what extent it is influenced by the degree of confidence [31, p. 550]. The answer will be given with a "yes" or "no" response.

Electroencephalograph (EEG). The rs – EEG will be conducted in a properly adapted room, which

will be quiet and dark. The participants should sit comfortably and they will be instructed to switch between the conditions “eyes open” and “eyes close” every five minutes for twenty minutes. They will be also instructed to relax, to try to release their minds from any thoughts and to move as little as possible. For the electrophysiological recordings, we will follow the same procedure as was applied in a recent study of Klados et al. [28], in which they used 57 active electrodes placed according to the 10 – 10 international system.

Intervention

As it has been already mentioned, the intervention will last six months, and it will consist of individual training sessions, once per week and with duration of one and a half hour. Between sessions, written material will be given for homework, which will contain ecologically adapted tasks (e.g., instead of a list of random words, a grocery list will be given). The purpose of the homework is for the participants to apply and practice the metacognitive strategies they will learn during the training sessions.

During the first session, participants will be provided with theoretical knowledge as well as with practical examples regarding the meaning and the role of cognitive strategies and MF. The purpose is for them to get familiar with the intervention’s procedure. The next session will start with a task. First, instructions for the task will be given. Then, participants will be asked to define the goal of the task and the steps they would have to follow in order to complete the task (planning). As soon as they finish the task they will have to evaluate their performance and whether it deviates from the task goal. If the outcome is in accordance with the initial goal, they will be given a new task (increased level of difficulty, same cognitive function) and they will be instructed to follow the same steps. If the outcome deviates from the initial goal the participants will be provided with a variation of the same task (same level of difficulty, same cognitive function) and an alternative cognitive strategy will be discussed in collaboration with the examiner and then applied in order to finish the task. At the end of every session, there will be a short discussion about the strategy or strategies that have been used and how they could be applied in different situations of daily life. At the beginning of every next session, there will be given some time to discuss and evaluate the previous days' homework.

Regarding the cognitive training, the participants will be asked to perform the same tasks. However, they will not receive any metacognitive enhancement and there will be no discussion about the application of cognitive strategies in different contexts or about homework evaluation.

Discussion

It is a fact that the average age of the world population has been significantly increased during the last decades. As a result, the need to deal with the aging health problems has been increased too. Dementia has dramatically increased and constitutes one of the main causes of health problems in elderly population [1]. In order to encounter this crisis, the scientific community makes a great endeavor in finding new, effective and targeted methods for early diagnosis and treatment of dementia-related cognitive impairment.

As previously reported, there is a great scientific interest in MCI, since it is considered to be a precursor of dementia [32]. Although numerous studies have focused on the CF and their decline in

MCI, yet only few of them have focused on the MF and their role in MCI. Metacognition plays a crucial role in the regulation of cognitive processes. Therefore, it is of great importance to investigate the possible interactions and relationships between metacognition and cognition – including ToM as the main dimension of the social cognition – in the most known and frequent sub-types of MCI.

The design of therapeutic interventions targeting generalization and maintenance of the results still remains a challenge for the scientists and the health professionals [33]. Although patients with MCI tend to score higher in neuropsychological tests after participating in a cognitive training, the improvement usually does not generalize to other domains. Conversely, recent research has suggested that therapeutic programs focusing on the enhancement of MF have positive and more permanent results, both in the general cognitive state and in the everyday functioning of older adults [13, 16, 19, 34, 35].

Despite the promising results of such interventions, there are only few of them that have been studied in MCI patients. Therefore, the proposed thesis suggests the application of an intervention that targets learning cognitive strategies through metacognitive strategies reinforcement. It is expected that this process will promote the generalization of the results of the intervention beyond the testing context and subsequently will improve general cognitive status and daily life functioning.

All authors declare that they have no conflicts of interest.

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Prof. Ioannis Tzafetas: Vienna Music Hall was built under the sponsorship of the Greek Nikolaus Dumba, architect the Danish Theophil Hansen. It's Golden Saal has the best worldwide acoustics. The Hall is in Dumbastrasse.

Cognitive training in community dwelling older adults via a commercial video game and an adaptation of the virtual reality platform FitForAll: comparison of the two intervention programs

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Abstract

Aim: This study aimed at examining whether Video Games (VG) and Virtual Reality (VR) programs are effective as cognitive training tools in community dwelling older adults. **Method**: The sample comprised a total of 19 older adults aged from 65 to 79 years. Participants were randomly divided into two groups according to the intervention program that they were submitted to. The first group was trained in a go-kart-style racing video game (Super Mario Kart) on the Wii console (n=9). Playing this type of video game has been found that secondarily endorses executive functions due to its technical demands. The specific executive abilities recruited haven't been established yet. On the other hand, the second group was trained using a virtual reality platform (FitForAll) adapted to train three specific executive functions (n=10). The two groups didn't differ in age, gender and educational level. In both groups the intervention included 18 sessions of about 40' each, over a period of six weeks (3 times per week). Measures of specific executive functions (inhibitory control, planning, task switching) were taken before and immediately after training, as well as one month after the intervention. **Results:** The findings indicated that the participants enhanced their performance in executive functions, after being trained in both intervention programs. However, VR application ended up to be more effective in the maintenance of this performance in the follow-up measurement. **Conclusion:** The increased performance in the follow-up measurement after VR intervention, could be attributed to both brain's plasticity and the specificity of training in terms of main executive functions' enhancement in the VR condition.

Keywords: Cognitive aging - Cognitive rehabilitation - Inhibitory control - Task switching - Planning

Introduction

Life's expectancy has been increasing towards the years. Specifically, in 1950 people were estimated to live 65 years, while in 2045-2050 this number is expected to be increased to 83 years [1]. This has led researchers to focus on the improvement of life's quality in aging [2, 3] by trying to maintain social participation and primarily cognitive function of older adults [4]. Even in "normal aging" (6^{th}-7^{th} decade of life) there is a slight cognitive decline [5] that affects memory and executive functions [6, 7, 8]. On the other hand, there is "brain's plasticity", that is, the brain's ability to adapt to the current environmental circumstances by changing its structure [9]. Appropriate practice and therapeutic intervention, which are relied on brain's plasticity, could delay or even avert cognitive decline. [10]. For instance, Lövdén, Brehmer, Li and Lindenberger (2012), who trained older adults to virtual navigation on treadmills over a period of four months, found that the hippocampal volume has remained the same in comparison with the control group, where a decrease was observed [11].

Hence, what cognitive training tries to do is to change brain's structure by mobilizing and activating latent areas of the brain. In particular, cognitive empowerment interventions seem to be effective not only on the improvement of healthy older adults' cognitive function [12, 13, 14], but also on maintaining this improvement up to 5 years [15]. Moreover, it seems to decrease memory loss in people, who suffer from dementia [16].

Nowadays, technology is closely associated to everyday life, giving researchers the ability to use its potential to perform cognitive interventions. Video games and virtual reality programs are two examples of how technology can be used as a cognitive training tool. Firstly, video games via exposing players to various stimuli can train various cognitive abilities, according to the game's category (strategy, action, racing, etc.). There are many research papers proposing that older adults, who have been trained by playing VG, showed improved performance in switching tasks, working memory, rotation, short term visual memory and other cognitive functions [17, 18, 19]. Taken the above into consideration, older adults may be capable enough in learning and adjusting in new environments. So, brain's plasticity is a continuous process that incurs even in aging. Virtual reality is defined as high -level computer interface, which includes real time simulation and interactions through multiple sensory pathways [20, 21]. It is a rather innovative practice, which uses computer software in order to combine visual, auditory and tactile sensations as simulation of different aspects of everyday life [22]. Kizony et al. (2012) trained 7 older adults diagnosed with Mild Cognitive Impairment (MCI) via learning metacognitive strategies in a virtual Super-Market for 5 weeks (10 sessions) [23]. The results have showed that 4 out of 7 participants improved their executive functions and intervention's benefits were transferred to other contexts. Moreover, Tarnanas et al. [24] used VR Museum as an intervention tool for patients with MCI and found improvements in cognitive functions, such as memory, attention and executive function.

Considering the aforementioned theory and findings, the present study aimed to examine whether VG and VR programs are effective as executive function training tools for the community dwelling older adults.

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

1. VG's intervention is expected to improve older adults' performance in tests requiring inhibitory control, task switching, and planning. This improvement would be maintained for 1 month (follow-up).
2. VR's intervention developed to recruit specific executive functions is expected to improve older adults' performance in tests requiring these functions, namely inhibitory control, task switching, and planning. Improvement would be maintained for 1 month (follow-up).
3. It is expected that older adults who have joined the VR's program would display higher performance in tasks measuring specific executive functions than older adults who have been trained by playing a commercial VG, as the VR program used in this study is adapted to specifically and systematically train these functions.

Method

Participants

Firstly, 64 older adults, who attend Open Care Center in Thessaloniki, Greece, were informed about the terms of this study, by whom 29 were eager to participate. But, 7 of them were excluded due to not fulfilling the requirements of the study. So, 22 community dwelling older adults started participating in the research, but during the process of the research, 3 of them left. Finally, the

sample comprised a total of 19 (9 women) community dwelling older adults, who participated voluntarily in the study. The sample was divided into two groups, depending on the intervention that each group was submitted to. The first group, which consisted of 9 participants, aged 65-78 years (*M*. =71,33, *SD*. = 4,60) was trained in a go-kart-style racing video game. Participants of this group belonged in two educational levels (EL): low EL (*n*=8, 0-9 years of education) and middle EL (*n*=1, 10-12 years of education). The second group, which consisted of 10 participants, aged 65-79 years (*M*. = 70,3, *SD*. = 5,03) was trained in the virtual reality program. Participants belonged in three educational levels (EL): low EL (*n*=4), middle EL (*n*=3) and high EL (*n*=3, ≥ 13 years of education). The two groups did not differ in terms of their gender, $\chi^2(1)= .656$, $p>.05$, age, $\chi^2(10)=.921$, $p>.05$ and educational level, $\chi^2(2)=5.295$, $p>.05$ (Table 1). At this point it should be mentioned that as far as the educational level is concerned, strict statistical criteria were applied, because of the potential inconsistency of the chi-square test, due to the small number of participants in each group of the sample. So, the *Monte Carlo* and the *Exact value* criteria were adopted and the respective indices were computed. Exclusionary criteria for potential participants were the presence of uncorrected hearing or/and visual loss and any other severe physical, psychiatric and neurological disease. The presence of depressive symptoms was examined by the Geriatric Depression Scale-15 (GDS-15). Participants, who scored more than 6 in this scale, were excluded from the sample [25, 26]. Additional exclusionary criterion was the existence of cognitive decline. A score lower than '23-24' in the Mini Mental State Examination (MMSE) is considered indicative of dementia symptomatology [27, 28]. In this study, each participant who scored lower than '27' was excluded in order to ensure that even mild cognitive decline was absent. Moreover, the Montreal Cognitive Assessment (MoCA) was administered [29, 30] not as a screening tool but in order to formulate a more accurate "picture" for the general cognitive ability of the participants in the study.

Table 1. *Participants' distribution according to age, gender and educational level and screening tests' mean.*

Intervention	Age	Gender		Education (years)			GDS-15*	MMSE**	MoCA***
	Range	Male	Female	Low	Middle	High	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Video Game (*n* =9)	65-78	4	5	8	1	-	0.77 (1.4)	28.9 (1.1)	25.1 (2.8)
Virtual Reality (*n*= 10)	65-79	6	4	4	3	3	0.9 (1.1)	28.7 (1.2)	26 (2.2)
Total sample (*N*=19)	65-79	10	9	12	4	3			

**GDS-15= Geriatric Depression Scale, **MMSE= Mini Mental State Examination, ***MoCA= Montreal Cognitive Assessment*

Measures

Delis- Kaplan Executive Function System [31]. This battery is created to examine higher-order cognitive functions supported by the frontal lobe (executive functions). It consists of nine stand-alone tests. In this study, 2 of them have been used. Their psychometric properties have been examined for the Greek adult population by two of the authors of this study in a series of previous studies [32].

1. D-KEFS Design Fluency Test (DFT) [31]. To examine participants' executive functioning as inhibitory control and cognitive flexibility (inhibition and task/rule switching), DFT was used. The task requires initiating problem-solving behavior, generating visual patterns, creativity, simultaneous processing in drawing the designs while observing the rules of the task and inhibiting previously

drawn patterns. There are three conditions: basic, filter (requiring inhibitory control), and switch. For all the conditions, participants were first shown a practice page with 3 squares, each of which contained dots. Participants had to create different patterns by connecting the spots using 4 straight lines within 60''. Here we used the score from the second condition, which tests the inhibitory control of the participants and the total score of the participants after completing the whole test, which was considered as an indicator of their cognitive flexibility.

2. D-KEFS Tower Test (TT) [31]. TT was used to examine planning as a combination of a series of executive functions, working memory, and spatial ability. Participants had to construct "towers" through moving disks varying in size across three pegs in the fewest number of moves by following two rules (1. not to put a bigger disk upon a smaller and 2. not to take two disks at a time). It is composed of 9 problems that assess visual - spatial planning as learning rules, inhibitory control, and working memory. In this study we used the participants' total score in this test as an indicator of their planning ability.

Intervention Programs

1. *Video Game – Super Mario Kart (Nintendo)* [33]. The equipment used for this intervention was a Wii console which consisted of a central processing unit, a wireless remote control- steering wheel and a 26''screen. Participants were seated in front of the screen and they were holding the steering wheel. They were supposed to finish the track by driving a car, while trying to beat their opponents. It was a customized intervention that lasted 18 sessions of 40' each, where the participants had to complete playing 12 tracks.
2. *Virtual Reality- FitForAll [34, 35].* This program was designed by the Department of Medical Physics Laboratory of A.U.TH. It is important to mention that the part of this program that was used for the terms of this research was adjusted to train specific executive functions. The equipment used for this program was a 32'' screen, a "Kinect" sensor and a laptop. Participants were standing in a 2-meter distance in front of the screen and the sensor. It was also a customized intervention that lasted 18 sessions of 40' each. During this time, participants had to complete 4 tasks that formulated as follows:

a. *Apple collection using only the right hand.* This task has 3 conditions. In the first condition, that examines *attention*, participants have to collect every apple that appears on screen in succession (5minutes). The second one that tests *inhibition* requires from the participants to collect the apples avoiding the rotten ones that appear at the same time (5 minutes). In the third condition, that examines *switching and inhibition*, participants have to collect alternately 2 types of apples (red-green) appeared on screen (5 minutes).
b. *Fish collection by moving the torso back and forth.* This task is composed of 2 conditions. The first one examines *attention.* Participants have to collect each fish appeared on screen (5 minutes). The second one that tests *inhibition* requires from the participants to keep collecting fish, while avoiding the sharks, which appear among them.
c. *Golf simulation by moving the torso in 4 different directions (back-forth-right-left).* This task is composed of two conditions. In the first condition participants have to throw the ball into the hole by moving their torso (5 minutes). This condition focuses on examining *attention*. The second condition is similar with the first one, but here participants have also to avoid the potholes that appear among the regular holes (5 minutes). In this condition *inhibitory control* is tested.

d. *Break Blocks Game simulation by moving the torso right and left.* This task has only one condition, which tests *attention.* By moving their torso left and right, participants moved the bar so that to hit the ball and break the bricks (5 minutes).

Procedure

The examination process started with the completion of the individual- demographics information and the signing of the informed consent form by the participants. Afterwards, the screening tests which ensured that the participants met the inclusion criteria were administered. As it was mentioned before, both intervention programs were based on customized examination. The battery was administered before, after, and one month after the end (follow-up) of both intervention programs. At this point, would be worth mentioning that before the start of each intervention program, participants were trained in order to become acquainted with the tasks of each program (Figure 1).

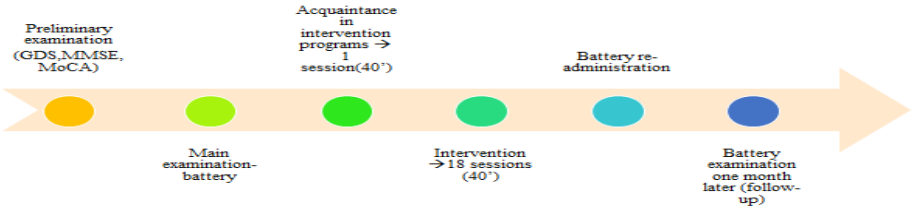

Figure 1. The design of the study

Statistical Analyses

The data were analyzed using the SPSS (v.22). Mixed Measures ANOVAs were conducted. Particularly, the group type (VG-VR) was defined as the between-subjects factor, and the measurements of the test (before-after-follow-up) as the within-subjects factor. Wherever the results were statistically significant, Repeated Measures ANOVAs were conducted, in order to define which type of intervention affected the most participants' performance.

Results

1. D-KEFS: Design Fluency Test.

a. 2nd Condition: Inhibitory control. Mixed measures ANOVA determined that participants' performance was affected by the type of intervention they were subjected to and also, the performance differed statistically significantly between time points, $F(2,34) = 7.672$, $p < .05$, $\eta^2 = .311$. Specifically, the Bonferroni correction revealed that the type of intervention affected participants' inhibitory control as there were found statistically significant differences between the pre-training and the post- training measurements ($p = .011$), and between the pre-training and the follow-up measurement ($p = .007$). Because of these results repeated measures ANOVA conducted for each intervention groups. As regards VG, results showed that there was not a significant difference in participants' performance between time points, $F(2,16) = 3.188$, $p > .05$, $\eta^2 = .285$. The same test conducted for VR showed that there was a significant difference in participants'

performance between time points, $F(2,18) = 24.100$, $p < .05$, $\eta^2 = .411$. Subsequently, Bonferroni test was conducted separately for the two interventions' groups. Training using VG improved participants' performance only from pre-training to post-training, $p = .012$. As far as VR is concerned, there was a statistically significantly improvement in participants' performance from pre-training to follow-up measurement, $p = .017$. However, there was also a tendency for slight improvement between pre-training and post-training, which, however, was not statistically significant, $p > .05$ (Figure 2).

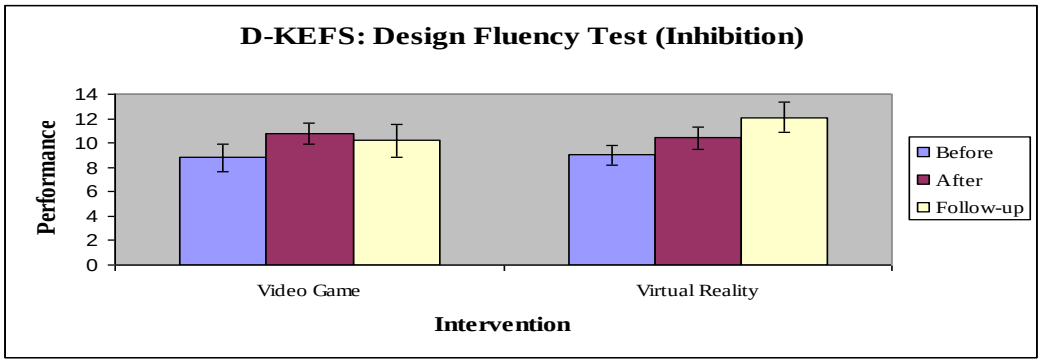

Figure 2. VG and VR participants' performance in D-KEFS: Design Fluency Test: Inhibition.

b. Total score: Cognitive flexibility (initiation, inhibitory control, & task switching). Mixed measures ANOVA with Greenhouse-Geisser correction showed that participants' performance was affected by the type of intervention and it differed statistically significantly between time points, $F(1.4, 24.5) = 9.670$, $p < .05$, $\eta^2 = .363$. In particular, the Bonferroni correction showed that intervention's type led to improvement of participants' cognitive flexibility, as there were statistically significant differences between the pre-training and the post- training measures, $p = .006$, and between the pre-training and the follow-up measurement, $p = .011$. Repeated measures ANOVA conducted to determine which intervention's type affected the most participants' performance. The results for VG showed that there was a statistically significant difference in participants' performance between time points, $F(2,16) = 3.863$, $p < .05$, $\eta^2 = .326$. The same was found for VR, $F(2,18) = 7.855$, $p < .05$, $\eta^2 = .466$. Afterwards, Bonferroni test was conducted separately for the two interventions. Training using VG improved participants' performance only from pre-training to post-training measurement marginally, $p = .056$. As far as VR is concerned, there was a statistically significant improvement in participants' performance from pre-training to follow-up measurement, $p = .037$ (Figure 3).

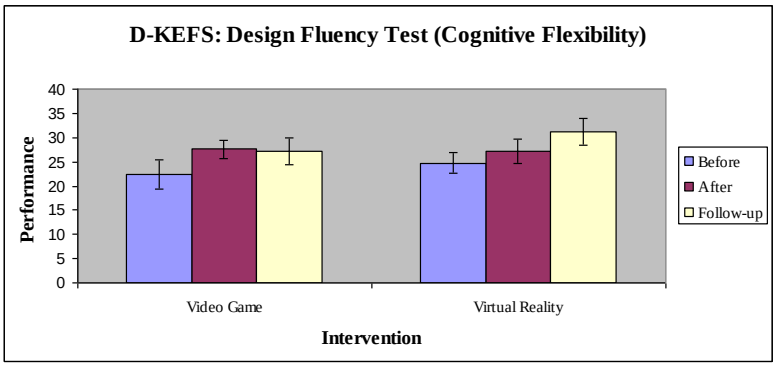

Figure 3. VG and VR participants' performance in D-KEFS: Design Fluency Test: Cognitive flexibility.

2. D-KEFS: Tower test: Total Score: Planning

a. Total Score. Mixed measures ANOVA showed that participants' performance was affected by

intervention's type and differed statistically significantly among the three time points, $F(2, 34) = 9.969$, $p < .05$, $\eta^2 = .370$. Bonferroni correction showed that the type of intervention affected in different degree participants' planning ability, as there is a statistically significant difference between the pre-training and the follow-up measurement, $p = .002$, and a marginally significant difference between the pre-training and the post- training measurements, $p = .052$. To determine which type of intervention was the more effective one repeated measures ANOVA was conducted. The results for VG showed that there was a significant difference in participants' performance between time points, $F(2,16) = 5.209$, $p < .05$, $\eta^2 = .394$. The same was found for VR, $F(2,18) = 5.066$, $p < .05$, $\eta^2 = .360$. Bonferroni test was conducted, separately for the two interventions. Training using VG improved participants' performance only from pre-training to follow-up measurement, marginally, $p = .052$. As far as VR is concerned, there also was a marginal significant improvement in participants' performance from pre-training to follow-up measurement, $p = .056$ (Figure 4).

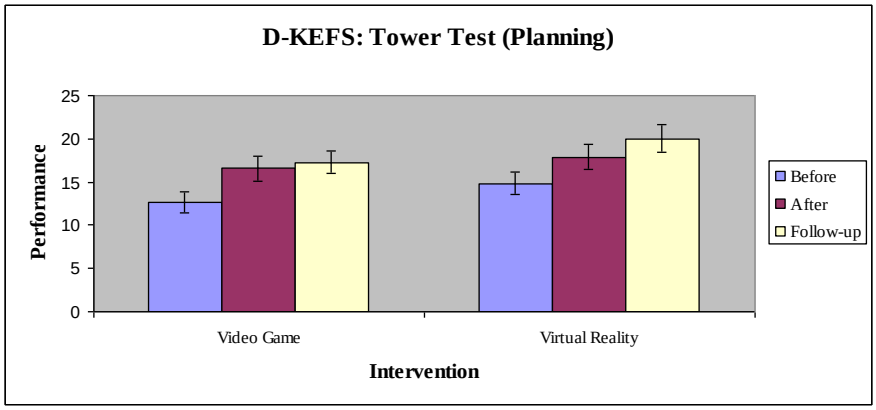

Figure 4. VG and VR participants' performance in D-KEFS: Tower Test: Planning.

Discussion

The purpose of this study was to examine whether a commercial video game (Super Mario Kart) and an adjusted part of a virtual reality program (FitForAll), would be useful as cognitive training tools for community dwelling older adults. This was tested by dividing participants into two intervention groups and examining their performance to a battery before, after and one month after the intervention programs (follow-up).

The first hypothesis of the study was merely confirmed, as VG's intervention slightly improved participants' performance, as estimated by the battery scores, but was not effective enough in maintaining the improved performance, as the follow-up measurement has shown. Particularly, inhibitory control was improved but not maintained, task switching was slightly improved without being sustained and lastly planning was slightly improved in the follow-up measurement. The second hypothesis was also merely confirmed, as VR program improved statistically significantly participants' inhibitory control and task switching only in the follow-up measurement. Planning was also improved but marginally in the follow-up measurement. Last but not least, the third hypothesis, as it is obvious from the above, was generally confirmed. Participants, who were trained on the VR program tended to maintain their improved performance even one month after the end of the intervention.

The findings could be interpreted by theories associated with brain's plasticity. Given that motor skills are critical for initiating neuroplastic changes, virtual reality programs that promote these skills

seem to be more effective in the improvement and maintenance of cognitive functions. In other words, VR programs promote brain plasticity by providing an alternative environment for practicing motor skills [36]. Moreover, some VR interfaces may be more effective because they are adapted to train specific cognitive functions, as working memory, learning, inhibitory control and task switching (e.g., FitForAll, VR Museum, etc.), in contrast with commercial VG that are not [24,34,35].

As far as VG intervention is concerned, it is assumed that they are also as effective as VR programs, with the important difference that the benefits acquainted through practicing with them, are not sustainable. This drawback may be compensated by continuous training.

Limitations and future research

There are some limitations in the study. The restricted nature of the sample should be noted. Also, the potentially short duration of both interventions (18 sessions) and the small period of time mediated the administrations of the battery (before-after-follow-up measurements) could be noted as limitations.

To conclude, it would be really interesting to examine how this intervention programs apply to other groups, such as people with dementia (MCI, Alzheimer's disease, etc.). Moreover, the duration of these interventions could be a possible topic of future studies

Conclusion

The hypotheses of the study were confirmed, as both intervention programs improved participants' executive functions. However, VR program seems to be more effective in maintaining the results of the cognitive training, as the follow-up measurements have clearly showed. The field of cognitive training via technology has not been yet completely discovered, hence, many studies related to this could be conducted.

All authors declare that they have no conflicts of interest.

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Brief review and research proposal about mind, dimensia, sleep and MCI

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Abstract

Aim: The purpose of the proposed study is to examine the relationships between sleep parameters, cognitive control and Theory of Mind (ToM) in patients with Mild Cognitive Impairment (MCI) and their cognitively healthy peers, in order to indicate how the pattern of these relationships are dynamically formed. **Method**: The present study will consist of (a) a longitudinal research project and (b) a randomized study of a personalized, non pharmacological intervention. Regarding the longitudinal research project, the same examination will be carried out in three stages, separated by an interval of ten months. In each stage, three participant groups (amnestic MCI n= 50 , non-amnestic MCI n= 50, cognitively healthy control group n= 50), will be examined with an actigraphy and self-reporting questionnaires (Athens Insomnia Scale, Stop - Bang Questionnaire, Pittsburgh Sleep Quality Index, Sleep diary), in order to collect both objective and subjective measurements of various sleep parameters. Additionally, they will all be given a series of tests (TASIT Test, Delis-Kaplan Executive Function System - D - KEFS, ect.) to measure ToM and cognitive control. Subsequently (b), two smaller sub-groups of participants with MCI (both amnestic and non-amnestic n = 10) will be selected in randomized way, which will then be divided, also randomly, in experimental and control groups. After assessing the level of cognitive control and ToM, the participants in the experimental group will participate in a personalized, non pharmacological intervention to improve their sleep, for a period of time respective to the identified disorder, while the participants in the control group will not. There will be follow-up measurements (assessments) of cognitive control and ToM right after the intervention, as well as three months later. **Conclusion:** The expected benefits are the identification of changes in sleep of patients with MCI, which could serve as markers of the progression to dementia, more so in specific subtypes. They are also about revealing the pattern of the relationships between changes in sleep and changes in ToM throughout the trajectory of cognitive decline, in order to make the development of effective interventions for their correction possible for patients diagnosed with MCI.

Keywords: Sleep - Metaphoric speech understanding - Dementia - Theory of Mind - Mild cognitive impairment

Introduction

Sleep

Sleep is a dynamic, energetic and complex situation, indispensable for our survival. It affects the normal functions of our organism. It is especially significant for the rest of both the nervous and the

muscular system, for memory consolidation, and for the restoration of cellular functions in the brain and the rest of the body [1].

The term “sleep” describes a normal, periodic idle state, during which a reduced reaction to external stimuli and subsequent reduced mobility of the skeletal muscles, of the metabolism and of the respiratory function is observed. Sleep is regulated through the homeostatic and circadian mechanisms [1]. The proper functioning of these mechanisms is easily affected by factors such as age, medication and various pathological and psychological diseases [2].

The modern lifestyle is the main reason why increasingly more people suffer from sleep disorders. Sleep disorders are frequent among the general population, as well as among special populations, such as the elderly, women, and patients with co-existing medical, neurological and psychiatric disorders [3].

Sleep in aging

The elderly, the older-old adult and the centenarian population is constantly growing worldwide, resulting in rapid increase of social, economic, and medical problems related to aging [4]. This fact has drawn the attention and the interest of specialists to examine the psychological, physiological and pathological processes connected to aging.

Regarding sleep, in particular, in advanced age, the disorders observed are usually due to (a) a reduction in the stages of NREM sleep (Non Rapid Eye Movement), (b) a reduction in the quantity of REM sleep (Rapid Eye Movement), (c) frequent nighttime awakenings, and (d) short duration of daily sleep [5].

There are two factors which contribute to the desynchronization of sleep-wakefulness cycle in aging: the first, it happens when the intrinsic 24hour rate which is regulated by the pacemarker activity of the superchiasmatic nucleus in the hypothalamus is not synchronized with the stimuli of the environment and the second it happens when the homeostatic process which is increasing the longer the individual has been awake is not working properly [6].

In general, the most frequent types of sleep disorders during aging are insomnia, hypersomnia, circadian rhythm sleep disorders, sleep related breathing disorders and parasomnia.

As a result of the aforementioned disorders, people of advanced age go to sleep earlier and they wake up too early in the morning. Nevertheless, due to social circumstances, they are forced to stay awake until late despite the somnolence, while they continue waking up early in the morning, experiencing, thus, daily, a “sleep deprivation” condition, with daily somnolence and problems of social and cognitive nature [7].

Sleep disorders in MCI

MCI is considered a transitional phase from cognitively healthy aging to dementia [8, 9]. While MCI differs from the cognitively healthy aging in the presence of objective decline in at least one cognitive area, as well as from dementia, since the functional impairment is minimal, there is overlapping in the two ends of the spectrum and the differential diagnosis becomes complicated [10]. The ability, thus, to make a prognosis and a diagnosis of MCI in its early stages, during which even reversing the progression of cognitive decline or delaying its adverse effects is considered feasible, is extremely important. What is just as important is the ability to differentiate MCI converters and no-converters [11].

At times, various cognitive criteria to describe the definition of MCI have been set, mostly by Mayo Clinic [10]. A consensus report by the International Workgroup on MCI highlighted the need to classify MCI into various subgroups, based on the nature of the cognitive decline exhibited by patients. The MCI where mnemonic deficits are prominent is defined as amnestic MCI, while when the prominent deficits are not of a mnemonic nature but concern one or more disturbed cognitive functions it is defined as non-amnestic MCI, with single non-memory domain or with multiple cognitive domain [12, 13].

Recently, research has been carried out comparing the prevalence of sleep disorders in various subtypes of MCI [14]. A considerably higher prevalence of nighttime disorders was exhibited by patients suffering non-amnestic MCI, compared to the patients suffering amnestic MCI [15].

Among the studies that research the prevalence of sleep disturbances, they found particular features between participants with MCI, those with normal cognition and AD patients. In a study using actigraphy in patients with naMCI found that greater number of wake arousals during the rest space were significantly associated with poorer nonverbal learning even after controlling for age [16]. Another study comparing participants with and without cognitive impairment and demonstrated that night time behaviors are more common in patients with MCI than in normal older adults [17].

The other study that used the polysomnographic to compare sleep and memory in MCI patients and older adults established some changes in sleep and memory. In sleep patients with aMCI spend fewer minutes in slow wave sleep than the participants in the control group and fast spindles were reduced in aMCI patients at F3- 4 recordings sites compared to controls. In memory, recall was worse in the in the MCI group than in the control group [18].

There are, therefore, indications highlighting the need for a deeper investigation of sleep disorders among the elderly diagnosed with MCI, as a possible early marker of cognitive disorganization.Taking into account that MCI diagnosis is primarily based on a neuropsychological assessment, it could be examined whether and to what extend sleep disorders contribute to cognitive decline, impairment in social cognition and to daily communication and the patient's interaction with other people [7]. Furthermore, any covariance of specific sleep disorders and of special dimensions of cognition could be a reliable marker of the degree of deterioration of the cognitive status and of the patient's daily functioning, as well as of their transition from MCI to specific dementia subtypes [19]. In that context, an area which – as far as we know – has not been investigated at all is the area of the possible interconnection (cross-sectional and longitudinal) between sleep disorders and Theory of Mind in MCI.

Theory of Mind in MCI

Theory of Mind (ToM), as a dimension of social cognition, was introduced by Premack and Woodruff (1978) in the context of their study, in which they tried to investigate whether apes were able to draw conclusions on the mental work of other creatures of their species. Since then, ToM has been the most significant as far as research is concerned, as well as the most studied – at least as to specific aspects – dimension of social cognition. ToM refers to people's ability to attribute mental states to themselves and to others, such as desires, intentions, feelings and beliefs, with the aim to bestowing meaning to and predicting behavior [20]. ToM is considered to have two broad dimensions: the cognitive and the affective one [21]. The cognitive ToM refers to people's ability to draw conclusions on cognitive situations, such as thoughts, beliefs, and motives [22]. The affective ToM refers to the

ability to draw conclusions on what a person is feeling [23]. The two dimensions do not always follow parallel lifespan trajectories for a variety of reasons, one of which is the dementia-related disorganization of the structures that support them [24].

Based on the majority of recent studies, aging is connected to selective deficits in the ToM, which cause considerable difficulties in social interaction and lead to low social participation [25]. It is not at all clear, however, whether those deficits are connected to the decline of cognitive control or whether they only concern ToM [26, 27]. The participants in this study seem, in general, to perform worse compared to healthy individuals, yet the decline occurs selectively. Total disorganization is evident in subtypes such as Behavioral Variant FTD (frontotemporal dementia)[14]. On the other hand, there are relatively few studies which have attempted to investigate what happens with ToM in MCI, and even fewer which have dealt with the association between ToM and sleep disorders in aging [28].

In a recent study, the researchers attempted to investigate a particular dimension of understanding speech transport, and in particular sarcasm, in patients with MCI compared to community dwelling controls with vascular risk factors. The results of this study indicated that MCI patients had significantly worse performance than the control group in simple sarcasm understanding [29]

The effect of sleep and sleep deprivation on the physiology of the human body, especially on brain structures that involved in cognitive and emotional functions, appears to be particularly important. Significant findings have been found about the positive effects of sleep, especially those in the REM sleep phase, on the regulation of emotions [30]. On the contrary, research has disclose that sleep deprivation may have serious consequences onto cognitive health [31].Sleep deprivation has been related with impairments in working memory, declarative memory, higher-order cognitive skills, divergent thinking, decision making and alertness [32].

The results of a study that examined the effects of sleep deprivation in their participants indicated significant impairment in the structures that support working memory and activation of the prefrontal cortex [33]. Another study that examined the effects of sleep deprivation but focused Aon the emotional intelligence of the young adult participants found decreases in intrapersonal functioning, interpersonal functioning, stress management skills, and behavioral treatment, together with increased internal reflection [34]. Hence it seems the sleep is more important for older adults, compared to younger adults, in order to preserve their cognitive and affective functioning at an sufficient level, to counterbalance the impairing effects of aging. In a study which have dealt with the association between ToM and sleep disorders in aging found that older adults had a significantly lower capacity to decipher basic emotions from dynamic visual cues compared to that in the morning and after night sleep [28].

Aim and hypotheses

With the above presented as a reference framework, and taking into account the need arising from the literature for research which will attempt to shed light upon the developmental trajectory of dementia-related cognitive decline in aging differentiation of dementia syndromes, as well as the need arising on a therapeutic/practical level for patients with MCI to maintain the ability to interact and socially participate, where possible, the main aim of the present thesis is “to assess the changes in sleep parameters in older adults diagnosed with MCI, compared to the respective sleep

parameters in cognitively healthy elderly people, and to examine the relationships between these parameters and the level of Theory of Mind". Since it has been claimed that changes in the levels of ToM in MCI are possibly connected to the decline of cognitive control, the aim of the proposed thesis is extended to examine the relationships among sleep parameters – cognitive control – ToM in patients with MCI and their cognitively healthy peers, in order to indicate how the pattern of these relationships is dynamically formulated.

Hypotheses

In this context, the hypotheses of the present study are as follows:

1. (a) Sleep disorders are expected to increase in patients with MCI, compared to cognitively healthy peers.

(b) Nevertheless, they are expected to differentiate qualitatively and quantitatively in patients with amnestic and non-amnestic MCI.

2. A highly negative correlation is expected between sleep parameters indicating disorder and the level of ToM in patients diagnosed with MCI, compared to cognitively healthy peers.

3. There will be a differentiation in the level and associations of sleep parameters and ToM abilities in people diagnosed with amnestic MCI and in people diagnosed with non-amnestic MCI.

4. A highly negative correlation is expected between sleep parameters indicating disorder and the level of cognitive control in patients diagnosed with MCI, compared to their cognitively healthy peers.

5. The correlation between sleep parameters indicating disorder and the level of cognitive control is expected to be different in patients diagnosed with amnestic MCI and in those with non-amnestic MCI.

6. (a) Cognitive control may influence the relationship between sleep parameters and ToM.

(b) The degree of influence of cognitive control on this relationship is expected to become stronger over time.

7. One month after the successful application of non-pharmacological intervention on sleep problems, it is expected that the participants in the interventions have improved cognitive control and the ToM abilities.

Method

Design

The present study will consist of (a) a longitudinal research design and (b) a randomized study of a personalized, non-pharmacological intervention. Regarding the longitudinal design, the same examination will be carried out in three stages, separated by an interval of ten months. In each stage, three participant groups (amnestic MCI, non-amnestic MCI, cognitively healthy control group), will be provided, in randomized way, with an actigraphy and self-reporting questionnaires, in order to collect both objective and subjective measurements of various sleep parameters. Additionally, they will all be given a series of tests to measure the ToM, and they will be provided with the tools to measure cognitive control. Structural equation models will be used to process data of the longitudinal study, so that changes and variations in consecutive measurements, as well as the relationships between them, can be revealed.

Subsequently (b), two smaller sub-groups of participants with MCI (both amnestic and non-amnestic) will be selected in randomized way, which will then be divided, also randomly, in

experimental and control groups. After assessing the level of cognitive control and ToM, the participants in the experimental group will participate in a personalized, non pharmacological intervention to improve their sleep, for a period of time respective to the identified disorder, while the participants in the control group will not. There will be follow-up measurements (assessments) of cognitive control and ToM right after the intervention, as well as three months later.

Participants

The participants in the study will be patients recently diagnosed with MCI (0 – 3 years since the diagnosis) who visit Neurological outpatients departments and Day Centres of the Greek Association of Alzheimer's Disease and Related Disorders. Cognitively healthy participants, will be older adult volunteers who live in the community. At the outset of the investigation, the full medical history and use of any medication will be recorded, as well as anthropometric data (gender, age, height, weight, neck, waist and hip measurements, education), smoking habits, and alcohol consumption. Any co-morbidities will be recorded based on the medical histories and strict exclusion criteria will be set. The psychological exclusion criteria are psychoses, depression, addictions and neurodegenerative diseases. In order to form the group of cognitively healthy elderly people, the potential participants will be tested on their cognitive function by the same psychologists via a complete neuropsychological battery.

Each group of the three groups of the longitudinal study will consist of 50 older adults, matched for gender, age and level of education. Each participant will be between 65 and 79 years old, with an education of 6 years or more, and their mother tongue will be Greek. The first group will consist of participants diagnosed with amnestic MCI. They will have been diagnosed with amnestic MCI syndrome after a complete neurological and extended neuropsychological assessment. The second group will include non-amnestic MCI patients [13]. The cognitive impairment of the above participants in the two patient groups will not be the result of emotional, mental or physical disorders. They will retain their Activities of Daily Living and, according to defined criteria, they will not be diagnosed with dementia. The control group will consist of cognitively healthy participants living in the community who do not exhibit symptoms of clinical depression, and do not have a history of psychiatric problems, a history of addictions, or a cognitive decline even in the form of subjective complaints of memory slips and cognitive failures.

The two groups participating in the second study will consist of amnestic (n = 10) and non-amnestic MCI (n = 10) patients, who will undergo a personalized intervention to improve their sleep, and a respective number of amnestic and non-amnestic MCI (n = 10) patients, who will act as the control group and will follow a program of personalized intervention to improve their sleep disorders once the study has been completed, and if they wish.

Measures

A combination of measurements, which will include neuropsychological tests and sleep parameters, will be used to assess all the participants in both studies.

Neuropsychological assessment

The neuropsychological assessment will be completed in two to three sessions in each stage of the

examination. First, the participants will be informed on the purpose of the study and they will have to give their informed consent on their participation. Then, the participants' personal information and demographic data and their full medical history will be taken, and, where necessary, they will be provided with screening tools. The tests and self-reporting questionnaires which constitute the main set of measurements have been examined on their psychometric properties and are succinctly mentioned below. The sessions, in each stage of the examination, will take place in the morning, will not be more than 7 days apart, and the meetings will be conducted by prior arrangement. The tools will not be provided with the same order every time.

Measures of sleep parameters. Actigraphy is a device which will be given to the participants of all the groups for seven days in every stage of the examination. This device is worn on the wrist just like a regular watch. It records data, the decoding of which helps to understand the participant's sleep-wakefulness cycle [35].

Moreover, the participants will fill out the following questionnaires, concerning the assessment of their sleep:

- Athens Insomnia Scale [36].
- Stop – Bang Questionnaire [37].
- Pittsburgh Sleep Quality Index [38].
- Finally, a sleep diary will be kept for two weeks, after they signed the informed consent.

Theory of Mind measures. Part A' of the study. The following basic aspects of the ToM will be assessed: (a) the ability to understand metaphorical and indirect speech, (b) the ability to perceive faux pas, and, (c) the ability to understand others' intentions and beliefs. All the ToM tests will be given in the form of stories, mixed with control stories which do not require anything but cognitive understanding. Furthermore, for every story in every ToM test there are cognitive comprehension questions, the answers to which will be used as exclusion criteria. All the tests come from Natsopoulos' battery [39]. Every test in the set consists of individual tasks of equal difficulty. To avoid any potential effects between practice and learning, as well as fatigue, 3 smaller sets will be created, with equivalent tasks.

Theory of Mind measurements. Part B' of the study. The subtest of emotion recognition through dynamic visual stimuli and the subtest of understanding sarcasm using the TASIT Test [40] will be used. To avoid any potential effects practice may have, 3 smaller sets of emotion recognition and understanding sarcasm tasks will be created.

Cognitive control measurements. To measure the basic executive functions, inhibition, cognitive flexibility, and working memory updating, a series of tests was chosen from the Delis-Kaplan Executive Function System – D – KEFS [41].

Personalized intervention to improve sleep. An increasing number of non-pharmacological therapies are now available for people with sleep disorders. The guidelines by the American Academy of Sleep Medicine recommend several non-pharmacological treatments as being effective [42, 43]. It is important for a clinician to have some knowledge of a number of these approaches, enabling a combination of treatments tailored to the individual requirements of the patient. The treatments will be chosen are depending on the sleep disorders that will be identified during the data collection process. Indicatively, treatments can include behavioral interventions such as increased daytime physical activity or other sleep hygiene measures such as decreased night-time noise or

light, avoidance of caffeinated drinks and alcohol or individual relaxation therapies.

Discussion

The age composition of the population of the Earth has changed considerably in recent years. The demographic aging has generated interest among scientists of almost every specialty, as new needs arise due to the long course of aging, needs which must be met effectively. Additionally, the increase in life expectancy has brought dementia at the medical and social forefront. The need to find methods of early diagnosis, prognosis, and therapy of this disease is also imperative, mostly due to the immense psychological and economic cost for the individuals themselves, their caregivers, and society in general.

In this context, the attempt to discern healthy from pathological aging and to codify their similarities and their differences has brought MCI at the forefront, as a possible transitional phase between the two [7]. Nevertheless, the cognitive decline seems to begin before MCI has been diagnosed, which is why the importance of finding MCI onset markers is one of the requisites of the present study, as is discovering any transition markers from MCI to specific dementia subtypes. These markers could be any changes in the sleep parameters, but also a covariance prototype of the sleep – ToM parameters and/or cognitive control.

Sleep disorders, as one of the most common neuropsychiatric symptoms, have not been investigated in most studies as autonomous symptoms in the context of aging, healthy or otherwise. The proposed thesis will seek to systematically work on sleep disorders in the 2 most common MCI subtypes, for two main reasons: firstly, to find markers of cognitive decline, relative to sleep parameters, and secondly, to examine the possible effects of sleep disorders on the patients' Theory of Mind, what could only negatively affect their everyday interactions with other people. In other words, sleep disorders can serve as a prognostic factor of cognitive decline among the elderly [44, 45, 46, 47, 48]. At the same time, the sleeping problems faced by patients with MCI must be detected and treated, so that their quality of life and their ability to develop and maintain social contacts can improve.

The proposed study aims to move towards this direction, using an original combination of neuropsychological tests and sleep parameters to better understand the image of this syndrome and to recommend a therapeutic intervention that would improve social functioning of people diagnosed with MCI.

The expected benefits are the identification of changes in sleep, which could serve as markers/diagnostic criteria of the transition to cognitive decline and/or dementia, more so in specific subtypes. They are also about revealing the pattern of the relationships between changes in sleep and changes in ToM throughout the trajectory of cognitive decline, in order to make the development of effective interventions for their correction possible for patients diagnosed with MCI.

All authors declare that they have no conflicts of interest.

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Creating and sustaining a social health care ecosystem: the case of LLM care services in Greece

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Abstract

In recent years, public health in Greece has been confronted with the burden of economic crisis, which has sit on top of other societal challenges like the elderly population constant increase. Impacts on social care services, employment and society overall, call for emphasis and attention upon creating suitable elderly healthcare services, that are flexible enough to cover for and face the aforementioned challenges while being based upon principles of scaling up strategies. To this extent, a Strategic Implementation Plan has been released by the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA) in order to outline best and modern practices that can contribute to better decisions on patient care, and more specifically that of elderly and vulnerable populations. Thus, creating new health care models,such as social health care ecosystems aligned with the aforementioned plan, begins to appear as a key factor for developments in this direction for Greece, but also for Europe. The aim of this paper is twofold. First, to present key elements of the establishment of the LLM Care (Long Lasting Memories Care) ecosystem, a new solution for active and healthy ageing, designed as a social ecosystem providing healthcare specialised for elderly and vulnerable populations. Second, to show how the main concept of LLM Care aligns with the principles of the strategic plan of EIP on AHA that demand for such initiatives to be scalable and operate as supportive ecosystems interconnecting the policy, business, social, technological, organisational and individual levels in order to be scalable and drive sustainable changes in social care while addressing key societal challenges. It is expected that inferences from this alignment exercise will be useful for a wide range of similar organisations and initiatives, in the interest of sharing best practices.

Keywords: Social HealthCare - Cognitive Training - Physical Training - Elderly - Vulnerable populations - EIP on AHA - Independent living - ICT

Introduction

Recent evidence shows that health status can be negatively affected by economic crisis, which often results in public spending and household income decreases [1]. It is therefore, imperative that, health-related issues are becoming more visible during the economic crisis in Europe [2]. More specifically, in Greece the support of a suitable planning unit with accessible information on health status is limited, without addressing the health-related needs of the population through actions in public health and primary health care [3]. Evidently, vulnerable groups like the elderly and the poor are affected the most in these situations [4]. Samples of vulnerable populations are continuously

increasing: for example, the number of elderly people as part of the demographic problem in developed societies (moderation of birth rates, longer life expectancy etc), but also other forms of vulnerable population like immigrants. To focus in elderly populations, it is European Union reported 19.2% of the population aged 65 or older and that number is expected to increase further in the next decades [5]. By 2050, the number of people aged 65 or older is expected to be 2.1 billion globally representing approximately 12% of the world population. This number is estimated to increase almost by three times compared to the one 40 years ago, there representing an impressing 16% of the world population [6]. Greek population seem to follow the European trend as in 2015 elderly people aged 60 or older represented 27% of the country's total population, while in 2050 is expected to be 40.8% [7].

Impacts on health and social care services for the elderly, should be assessed in combination with the increased needs for public spending on pensions, healthcare, long-term care, while expenditure on long-term care is expected to double by 2060 [8]. However, financial incapacity to cope for the aforementioned burden calls for attention by European Union states in order to ensure the sustainance of full health care services to vulnerable people. To this extent, new methods and ways have to be developed in order to address these needs for social health care and social insurance. Thus, the notion of promoting the active and healthy ageing (AHA) concept emerges as a likely resolution.

The main scheme of AHA as defined by the World Health Organization (WHO) includes the process of optimizing opportunities for health to improve quality of life as people age. In 2012, the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA) was established to promote innovation for ageing well by involving 74 regional and local organizations that have been defined as Reference Sites [9]. EIP on AHA focuses on restructuring health and social care services by involving development and testing of innovative solutions, in order to implement the most successful practices and allow for their cost effectiveness and sustainance.

In this context, Information and Communication Technologies (ICT) seem to play a central role in overcoming the aforementioned challenges and offerring a tremendous potential to enable vulnerable people to remain healthy and socially engaged thereby providing better quality of life. The definition and exploitation of best and most modern practices, therefore, becomes a key issue, as it can contribute to better and informed decisions in social care. For this reason, the idea of creating new health and social care models, by exploiting notions of social healthcare ecosystems, emerges as an attractive option for Greece but also for Europe.

The term "ecosystem" describes basically a community. In ecology, as well as, in computer science relevant research has studied systems consisting of organisms by using methods of production, exchange, investigation and storage [10]. Both sciences utilise methods to study the condition of a system, which is defined as the set of variables necessary to form its complete picture of every moment. The concept of stability is considered to be a critical feature as it is used to describe the ability of ecosystems maintained independently, and to cope effectively with any disturbances to normal operation. Thus, every single part of the whole puzzle can be easily managed and organized in order to provide better care delivery.

The ecosystem approach introduces new challenging opportunities for involved stakeholders in order to create value by using information technologies, services, and solutions that are able to be interconnected delivering better health care services to more people at a reasonable cost.

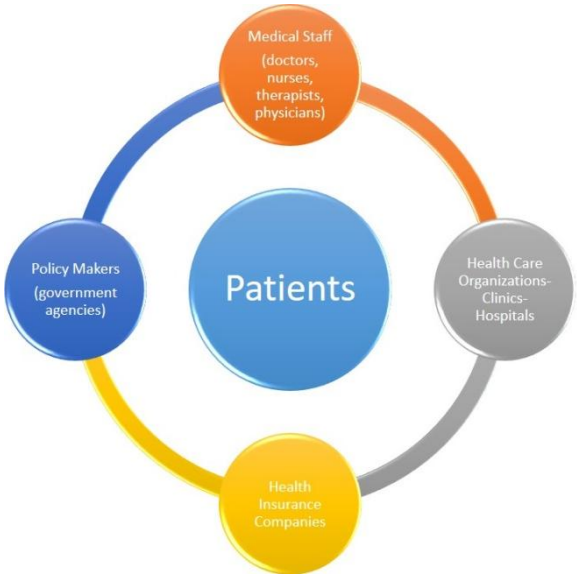

Figure 1. Involvement of different stakeholders for a patient-centered care ecosystem

The ecosystem consists of various collaborations (operators), such as medical staff, social and healthcare organizations, regional authorities, health insurance providers and policy makers, who can interact and work together in this social healthcare ecosystem to create innovative products or services through solutions like remote monitoring, connected health measurement devices, cognitive and physical training etc [11, 12].

Physical and cognitive training systems tackle quality of life deterioration among elderly or other people in need (cognitive and physical impairment and frailty) and there seems to be an urgent demand for new products and services in this direction. Collaboration of the technology actors (e.g. industry), governmental (and non-governmental) bodies facilitating social care provision, with research actors (e.g. universities) may give rise to sustainable social healthcare systems.

The current piece of work aims at presenting a case study of a social health care ecosystem addressing the needs of the most vulnerable segments of the population that is LLM Care [13]. The aim of this paper is twofold. First, to present key elements of the establishment of the LLM Care ecosystem, a new solution for active and healthy ageing, designed as a social ecosystem providing healthcare specialised for elderly and vulnerable populations. Second, to show how the main concept of LLM Care aligns with the principles of the strategic plan, recently released by EIP on AHA. The latter demand an operational interconnection of policy, business, social, technological, organisational and individual levels in order for such initiatives and ecosystems to be scalable and drive sustainable changes in social care.

So, the structure of this paper is as follows. In the following paragraph, a description of LLM Care key innovation elements is provided. Then, the main concept of LLM Care ecosystem is presented, aligning with the five steps for setting up an effective European scaling up strategy according to the plan of EIP on AHA.

Background: the LLM Care ecosystem and its innovation features

The Long Lasting Memories-LLM Project (2008-2012) [longlastingmemories.eu] came as a response

for wellbeing in the field of ICT, providing evidence based interventions by combining cognitive and physical training to improve cognitive functions (memory, attention and executive function) along with important physical ones (aerobic capacity, strength, balance and flexibility). Experiences and outcomes from the implementation of LLM, confirm viability of approach as proof of integrated care innovation concept that directly builds on local needs and variation [14].

The Long Lasting Memories Care - LLM Care [llmcare.gr], as an expansion of LLM, comprises of the key instruments to enable an ecosystem for social health care. Healthcare professionals, government administrations, healthcare institutions, patients, informal givers, facilitators, or other relevant stakeholders have all been interconnecting by interacting together with a mission to improve the quality of care. This approach promotes the continuously collaboration and knowledge sharing across the ecosystem by placing patients at the center of the health care. Taking into consideration the needs of professionals (increased knowledge, skills and collaboration), patients and carers (personalised care, care coordination, continuity of care), the healthcare ecosystem (local level, cost-effectiveness and sustainable approach) should be easily adopted in order to cope with current and future changes by involving new players.

LLM Care ecosystem provide high quality, sustainable health care by using an integrated platform of technological achievements in the field of computer-aided physical/cognitive training and ambient assisted living (AAL) solutions. It incorporates two interoperable components, the Physical Training Component (wFitForAll) and the Cognitive Training Component (BrainHQ) [13]. wFitForAll a web-based application (wFitForAll) using a modern controller (Microsoft Kinect) for healthcare monitoring and game-blended exercises and interventions [15] [16]. It offers specific exercises within an engaging game environment aiming at promoting physical exercise protocol adherence [17] [18]. BrainHQ is a specialised software designed to support cognitive exercises that was developed by the Posit Science [19] [20]. It is a fully personalised and adaptable cognitive training platform. BrainHQ is based on principles of neuro-aesthetic enhancement and brain plasticity and provides the opportunity to speed up and sharpen auditory and visual processing of the brain.

Methodology

The Strategic Implementation Plan released by EIP on AHA contains five main steps to set up an effective European scaling up strategy (Figure 2) [21]. To be able to move at a comprehensive scaling-up strategy, in which active and healthy ageing approach based on innovation can be implemented, one needs to carefully examine these steps. In this paper, each of these steps in taken in turn, and LLM Care and its features is passed through the step's lens, in an attempt to infer alignment or not with it. Should all principles of the strategic plan be met, LLM Care would be considered as a sustainable and scalable ecosystem, shaped up to address the societal challenges identified by and studied within EIP on AHA.

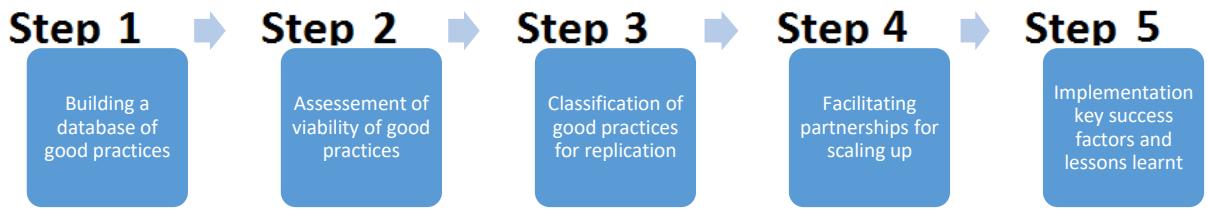

Figure 2. The 5-step model for an effective scaling up strategy [21]

Building a database of good practices: The LLM Care ecosystem

The first step, according to Strategic Implementation Plan is the collection of examples that contain the needs to be addressed in order for ageing people to stay active, independent and healthy. Action Groups and Reference Sites are formed to reveal a picture of innovative practices across the EU, as well as to find the key elements of a successful approach that could be transferred or copied by others.

The proposed health care ecosystem (LLM Care ecosystem), connects social, technological, organizational and individual levels in order to drive a sustainable change by involving public and private sector partnerships. Thus, innovations applied for a successful active and healthy ageing ecosystem have been introduced to examine the effective ways for addressing people's needs. Such concepts include links and interactions among health care facilities for elderly and vulnerable people. Daily care centers, rehabilitation centers, residential homes, municipality centers are some of the institutions that trust and collaboration has been built among their members and scientific group. Besides this, some of the groups' research outcomes (screening and assessment, serious games, pilot sites' logistics and management) have been commercialized and distributed by a network of experts (constituting the LLM Care entity) within Greece. On top of this, a wider network of stakeholders has emerged around the LLM Care product and two living labs have been installed in a nursing home, as well as in the Medical School of Aristotle University of Thessaloniki (Figure 3).

Figure 3. LLM Care Network of stakeholders and Active and Healthy Ageing Living Labs

Assessment of viability of good practices: The AHA Living Labs concept

This step of strategy proposes the assessment of the viability for scaling-up by using comparability frameworks, such as that coming from randomised controlled trials. Each system's characteristics and indicators of efficiency are identified by comparing systems on a larger scale. This approach helps not only to relate practices to each other, but also to identify the characteristics of each practice and system.

Visited constantly (over the year) by different people, the Thess-AHALL (Thessaloniki Active & Healthy Ageing Living Lab) was established to foster the early involvement of elderly and vulnerable people (the customers) in the development, as well as commercial products evaluation [12]. Special attention is paid in the usability, acceptability, perceived ease of use and perceived usefulness of seniors towards ICT usage. Thus, the LLM Care ecosystem contains an overall framework in which system's characteristics and indicators of efficiency can be identified. The most important factor for the creation of an ecosystem is the constant improvement of sustainability and efficiency of social and health care systems. Consequently, promoting and enabling citizens to maintain healthy, active and independent living style, while aged, is the main goal of such a concept.

Classification of good practices for replication

The next step of the proposed strategy contains the classification of good practices intended for replication. Thus, good practices should be classified according to feasibility and contextual factors, as well as the characteristics of the system that allow the transferability and adaptation to local conditions.

In this direction, the Day Care Centre of Municipality of Papagou-Cholargou (DOKMEPA) was joined the LLM Care ecosystem, after its first launching to the market. DOKMEPA integrated the basic instruments for physical and cognitive improvement and being presented as a replica of the LLM Care infrastructure. Thus, as suggested by the protocol of LLM Project, DOKMEPA performed neuropsychological tests to assess the participant's generic cognitive status as well as other specific cognitive domains (verbal memory, executive functions, independent living, etc.). Participants performed specific exercises for 1 hour per day, three times per week for a total duration of 10 weeks [22].

Moreover, a replica of Thess-AHALL [12] has been installed in a care center with senior residents in Thessaloniki. This living lab is a replica of the successful Active and Healthy Ageing Living Lab in the group's premises where co-creation and human center design are promoted. With such processes, successes, as well as mistakes can easily be identified saving time and avoiding duplications leading to the improvement of solutions. By creating such infrastructures, the relative influence of health systems on health outcomes can be determined covering the gap between the policy changes and the impact on health outcomes. Other determinants have to be taken into account for good practice adjustment to the local levels.

Facilitating partnerships for scaling up

For a successful scaling up, collaboration among the interested partners needs to be established in order to adopt the innovative solution. Thus, LLM Care network is consisted of the participation of different institutions, daily care centers, rehabilitation centers, residential homes, municipality centers that can provide valuable solutions to address the needs and gaps. The idea of rendering local authorities capable of delivering social care with new technologies and essentially doing research consists best practice and social innovation. By this way, the diffusion of good practices can be achieved, aiming at sharing knowledge, objectives and programs for the deployment of innovations in the domain of health and health care.

Implementation key success factors and lessons learnt

According to the Strategic Implementation Plan, a framework strategy of several steps of scaling-up

has to be implemented. A good understanding of the context where scaling-up will occur and the consciously evaluation of needs have to be determined, as well as a strategic plan for deployment is required, with a well-defined roadmap, costs assessment analysis and budget. Performance monitoring and evaluation of the service should be embedded from the start, to provide the collection of high quality evidences.

LLM Care ecosystem enables the collaboration of healthcare professionals, government administrations, healthcare institutions, patients, informal givers, facilitators, or other relevant stakeholders in order to address their specific needs with a mission to improve the quality of care. Continuing evaluation and feedback of the provided services include strategies to ultimately provide benefit for patients and informal carers, and society as a cost-efficient and sustainable approach. Thus, timely and accurate monitoring information is collected as considered to be important for successful adaptation.

The idea of rendering local authorities capable of delivering social care with new technologies and essentially doing research consists best practice and social innovation. Thus, helping for scaling up viable good practices, as well as improving the viability of similar practices. Each partner has its valuable expertise to analyze the local needs to adapt them to the local setting.

Discussion

Since the elderly population is constantly increasing, impacts on social care services, employment and society overall have been occurred. This growing demand in Greece, but also in Europe, leads to the restructuring of health care services. Thus, demographic transition ideally require shifting to the preventive health care, so as to address the needs of the elderly population [23]. Achieving high value for patients is considered to be the overarching goal of health care delivery [24].

The need for adaption to this growing demand lead to the establishment of new health care models, and more specifically the creation of social health care ecosystems aligned with the Strategic Implementation Plan of EIP on AHA. The main concept of LLM Care ecosystem aligns with the principles of this plan that demand for initiatives to be scalable and operate as supportive ecosystem by interconnecting the policy, business, social, technological, organisational and individuals in order to drive sustainable changes in social care while addressing key societal challenges. Following this direction, LLM Care ecosystem appears to be a crucial instrument for active and healthy ageing, designed as a social ecosystem providing healthcare specialised for elderly and vulnerable populations.

In the new age of healthcare ecosystems, the involvement of different stakeholders seek to deliver the highest level of patient care. Thus, information technology is on the top of such health care services by empowering the collaboration and knowledge sharing of stakeholders in order to improve care and independent living. Thus, new solutions for active and health ageing can be generated challenging EU and worldwide by creating new opportunities for innovation in Health Care domain. The active co-operation of the health and social health care providers and individual users in the ecosystem is considered to be essential.

All authors declare that they have no conflicts of interest

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Out-of-class vs. classroom-based learning: which is the best way to master a foreign language?

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Abstract

Mastering a foreign language entails becoming acquainted and gradually possessing features of a linguistic code which is different than one's mother tongue. Over the years various teaching approaches and educational theories have been implemented each boasting a new trend, each suggesting a new learning path. What has recently attracted scientific interest is the actual location where foreign language learning occurs. Where the learner is, i.e. inside or outside of a classroom is interconnected with the approach employed to master the target language. Typically, any kind of learning is associated with a classroom, a teacher, peers, and a formal curriculum. However, a classroom is not the only place where learning may occur. Out-of-class learning has always been happening but required an effort (e.g. travelling to a foreign country for leisure or on purpose, taking up a 'teach-yourself' language course etc.) and was not widely affordable. The advances in technology have undoubtedly facilitated access to an infinite source of authentic material in many languages expanding the horizons and broadening the possibilities of autonomous learners. Nonetheless, being an out-of-class student requires much more inner force in order to preserve the willingness to learn and overcome difficulties which are normally dealt with within a typical classroom setting. According to recent research, autonomous learners have attained high levels of language proficiency outperforming their in-class counterparts, which challenges formal classroom-based teaching methodology. Irrespective of the learning setting, however, the key to a learner's aim is motivation. It is the fuel that urges learners to excel at their endeavour. What if the foreign language learners were older adults diagnosed with Mild Cognitive Impairment?

Keywords: Foreign language learning - Autonomous - MCI

Introduction

When referring to foreign language (FL) learning, the connotative image which is almost automatically evoked is that of a classroom, the dominant language learning context [Sockett, 2014]. This traditional imagery is associated with the dynamic presence of a teacher and is accompanied by a group of peers, series of textbooks, CDs, DVDs, even interactive whiteboards for the more technologically equipped FL settings. Even though the classroom is definitely not the sole environment where FL learning may occur, it is due to the scientific focus on how FL are dealt with within that confined space that the relevant connotations have been created.

However, the long-standing need to communicate with people speaking different languages has not led to the implementation of FL courses. On the contrary, it has induced FL learners to become inventive in order to acquire the target language by employing various means and in different settings, none of which is necessarily formal. The advances in technology, the concomitant affordances and popularity of the Internet, and the inevitable rise of English as 'lingua franca' in the digital world has led to a reinvention of FL learning beyond the classroom. Across the Internet, autonomous learners have infinite possibilities to choose their channel of language acquisition and select an authentic material which may produce better linguistic results than traditional FL learning. This is particularly true of the young people around the world, who have grown up almost genetically predisposed to master the digital language of this era, being the "digital natives" of the 21st century [Prensky, 2001].

Aim

This paper aims to illustrate the importance of learning English as an FL particularly nowadays following the dominance of the language over the digital world. Moreover, it aims to inform readers on the different ways in which learners acquire an FL, with a particular focus on informal language learning. Additionally, it expands on the notion of learner autonomy and its pivotal role in innovative practices in language education. It further attempts to link the theories of language learning and teaching to Mild Cognitive Impairment seeking to expand the readers' understanding and suggesting new insights in the under-researched field of older adulthood.

Methods

The authors selected articles which would substantiate the delineated aims of this paper. They attempted to cite articles grounded in solid theories of learning and teacher bridging them with current practices and projecting them onto older adult learners of an FL. Obviously, the works cited needed to originate from various disciplines in order to tackle the aim set. The purpose was to try and prove that the areas of language learning and mild dementia though seemingly unrelated may constitute a challenging research field.

The English hegemony

Why is English the language *par excellence* any non-English speaking person should absolutely learn? According to Gramsci [in Jackson Lears, 1985] "language […] is a totality of determined notions and concepts and not just of words grammatically devoid of content". Gramsci realized that, through language, a group of people may firmly establish their "prestige" and "cultural leadership", rendering it an almighty political asset to each user. Evidently, when learning an FL, especially one which carries great weight, one becomes acquainted with its centrality and sovereignty. The explicit use of a certain FL or even the conscious choice of a variety of that language may exert influence on the speaker's social status. Within the English language there exist two major variations, namely British English and American English. The former is generally regarded as more prestigious while the latter is thought of as more informal. In a relatively recent study, Norwegian adolescent learners of English as an FL switched between British and American English pronunciation depending on how they wished to present themselves towards their peers [Rindal, 2010].

A powerful means of experiencing the cultural hegemony of a language is through its cultural

artefacts, such as literature, music, and films, which are publicly projected by means of the media and influence language users' everyday life unconsciously. In particular, media technologies, such as English-language subtitled television, popular music, and computer software have been favouring the incidental, and sometimes the intentional, language acquisition [Kuppens, 2010]. The rapid expansion of the Internet and its vast accessibility on various handheld devices, apart from personal computers or laptops, has resulted in English language learners being exposed to the language constantly, not to mention through highly popular websites, such as YouTube, Facebook and Wikipedia [Sockett, 2014]. The digital world is merely a 'click' away; one does not need to travel to London to speak English nor do they need to move to New York to work for an American firm. Literally, endless possibilities are at hand. Two basic skills are needed: digital and linguistic competence, both in English.

Formal vs. informal, learning vs. acquisition, then vs. now

Scientists have concerned themselves with the distinction between the two types of language learning settings, i.e. formal vs. informal, since at least the 1970's [Krashen, 1976]. Artificial vs. natural or formal vs. informal contexts have been related to classroom and out-of-class environments respectively. Both linguistic environments may affect FL competence in different ways. So, a further distinction was drawn which differentiated between language acquisition and language learning. Language acquisition was connected to a process of extensive exposure to the target language over a critical period which led to its unconscious knowledge and ultimately yielded linguistic competence. This process was thought of as pertaining by and large to young children and was achieved in informal settings, which provided the necessary input. On the other hand, language learning denoted the conscious attempt to master the target language by means of explicit instruction of linguistic rules and constant feedback on behalf of the tutor, which led to conscious knowledge and learned competence. This second process was largely reserved for adults and was only plausible and increased within a formal setting, i.e. a classroom.

Reviewed studies in Krashen [1976] seem to unanimously highlight the efficient contribution of formal training to second language mastery while denoting that informal exposure to the target language was not equally effective. It was thus argued that in order for informal contexts to be significantly influential, they should provide intensive exposure to the linguistic material. Moreover, according to research outputs, the classroom was proclaimed to be the locus of both acquisition and learning, considering that it offered the possibility of almost pragmatic and utterly instructed language use simultaneously. Finally, researchers agreed on both adolescents and adults being able to acquire an FL in the sense of informal exposure to it, since the critical acquisition period was over [Lightbown, 1985].

At the present time, acquisition and learning are used almost interchangeably, since acquisition means the learning or development of a skill and learning means the acquisition of knowledge or skills [Oxford Dictionary of English, 2015]. Henceforth, these terms will be employed as adjacent ones. Additionally, learning, in general, has been attributed a three-fold dimension and is normally differentiated into formal, non-formal, and informal, according to its organisation and structure in terms of learning objectives, time and learning support [Official EU Journal, 2012]. Following this categorization, formal learning occurs in a relevant setting, abides by a curriculum, and usually aims at the acquisition of a certification. On the other hand, non-formal learning refers to targeted activities

which improve specific skills of the learners and are usually promoted as part of in-service training. Lastly, even though informal learning is not organised in any way yet its outcomes are indeed acquired, though not on purpose. Interestingly, these learnt skills significantly affect the learner's daily activities and interests.

The same categorization may be applied to learning languages. According to Sockett [2014], formal language learning implies any physical or virtual educational setting where learners are trained in language mastery. Non-formal learning occurs when a learner uses learning resources (such as textbooks, CDs, DVDs, websites, etc) outside an academic context. Thanks to the affordances of the Internet these resources have vastly expanded to provide the user/learner with the opportunity to harness the power of social networking in order to master an FL. Obviously, in informal learning the Internet-based resources used by the learners are not educationally oriented nor do they form part of any systematic approach to language acquisition. The intended outcome is largely achieved unconsciously and heavily depends on the learner/user in terms of time dedication and frequency of exposure to the target language.

Learner autonomy

The concept of learner autonomy in language education dates back to the 1980's and Holec [in Benson, 2007], who equated autonomy with "the ability to take charge of one's own learning". This seminal definition was further enhanced by Dickinson [in Sockett, 2014], who provided an outline of eight criteria which differentiated the various degrees of learner autonomy or language learning types. These criteria include the decision to learn; method of learning; pace; when/where; materials; monitoring; internal assessment; external assessment. Scholars have hence attempted to provide finer nuances of the original conceptualization and delineate the profile of autonomous learners.

The decision to engage in the language acquisition process and to be responsible for the learning outcome [White, 1995]; the use of self-instructional techniques and methods and the realization of the quite specific role in this internalized process; the ability to disengage, think critically, make decisions, and be independent [Little, 1999], all seem to be imperative traits of autonomous learners. Over the course of years and due to the affordances of technology, the concept of learner autonomy has been linked with the use of digital products, particularly with respect to FL mastery. Undoubtedly, thanks to technology, FL learners have been given the chance to interact with native speakers, make appropriate linguistic choices depending on the social context, and practise the language in varied ways [Reinders & White, 2011].

Learner autonomy and informal way of learning seem to be interwoven, especially when informal is equated with online resource use. The cyberworld calls for interdependence and interaction between its users/learners and the outputs can be highly creative, collaborative, rewarding and motivational [Ushioda, 2011]. So long as the users/learners are committed to the FL target by means of engaging in appealing activities, the unconscious path towards FL mastery will be smooth, enjoyable, and purposeful. The mobile Internet-accessible devices which are readily available and constantly updated provide their users with feedback which enhances motivation and enjoyment in pedagogically-oriented activities or applications [Golonka, Bowles, Frank et al., 2014].

Such an experiment seeking to examine the learning effectiveness of motivational theory with the use of mobile technology was recently conducted in Taiwan [Chang, Chang & Shih, 2016]. It was shown that the students who received motivating feedback on their smartphones experienced

confidence and satisfaction while using the FL to a much higher degree than their non-motivated peers. Very recent research has also shown that young adult fully autonomous self-instructed learners of English as an FL surprisingly outperformed their matched classroom-instructed peers in FL mastery on a large battery of linguistic tests, which examined aspects of the language typically and solely taught within the classroom [Cole & Vanderplank, 2016]. Apparently, the naturalistic, out-of-class, informal language learning, which deploys Internet resources, seriously challenges classroom-based practices, methodologies, and tangible outputs, though further research is required to corroborate the new facts.

MCI & FL learning

Most people, over the course of their lifetime, show a gradual cognitive decline, mainly concerning mnemonic function. This cognitive impairment is usually minor and does not affect the person's functioning. However, when the cognitive decline exceeds the limit of normal ageing and is perceived by those who experience it and occasionally by their relatives, this condition is termed Mild Cognitive Impairment (MCI) which has been in the spotlight of research [Petersen, Roberts, Knopman et al., 2009]. MCI has scientifically been designated as an intermediate state of the cognitive function between normal ageing and dementia [Petersen, 2011].

The existing pharmacological interventions have not been able to delay the progression of MCI to dementia. Accordingly, there has been a growing scientific interest in non-pharmacological interventions whose aim is to enrich the cognitive reserve, through the mental empowerment of the patient, but also to reduce the progression rate of MCI to dementia [Cohen-Mansfield, 2005; Robinson, Hutchings, Dickinson et al., 2007; Tsolaki, Kounti, Agogiatou et al., 2011]. The notion of cognitive reserve means that the brain is attempting to deal effectively brain damage by using learnt strategies or by resorting to more versatile options. Recent studies have shown that lifestyle changes, even in old age, may enrich the cognitive reserve. Unquestionably, it should be clinically proved which combination of such activities and in what time leads to more normal ageing [Stern, 2012].

One way to enhance the cognitive reserve, while attempting a non-pharmacological intervention in patients with MCI, would be FL learning [Antoniou, Gunasekera, & Wong, 2013], a process which would expose the brain to language and communication environments [Blakemore & Frith, 2005]. Throughout the lifespan, cognitive abilities reshape the mind architecture by means of development, adaptive abilities, and functioning [Bialystok, 2011]. 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 [Marcotte & Ansaldo, 2014]. Brain plasticity has additionally been proved to assume a protective role against neurodegenerative diseases such as Alzheimer's disease since it preserves cognitive functions [Bialystok, 2011]. Presumably, FL learning would prove beneficial to people with MCI.

Older adults constitute a non-typical population in research as far as their language learning aptitudes in second language acquisition are concerned, which accounts for the rather limited research in this field [Mackey & Sachs, 2012]. What has attracted the scientific interest is the profile of bilingual speakers, the way bilingualism preserves their cognitive functions throughout the lifetime, as well as the protective effect of bilingualism against the onset of dementia symptoms [Bialystok,

Craik & Luk, 2012]. Consequently, it would be interesting to assess the evolution of MCI in older adults, native speakers of a language such as Greek, while learning English as an FL, bearing in mind that the two orthographies are sharply different.

Which is the best method to teach an FL to older adults with MCI? How can they best learn: in the classroom or online? Is the traditional formal context more familiar or would they perform equally well in the comfort of their home? Could MCI learners of an FL become fully autonomous self-instructed learners? Or perhaps a joint attempt might bridge the gap between formal and informal learning?

It is only logical to assume that MCI older adults would prefer a formal setting and traditional methodology in order to be trained in an FL. This would be mainly due to psychological reasons since the whole context would be reminiscent of their own schooling years when what it is now referred to as formal teaching was being established. Additionally, because FL learning is an activity associated with anxiety for any student regardless of age, these learners would feel more comfortable with the physical presence of their teacher. Responding to the personality and the approach of the tutor, of course, they would attempt to establish a rapport with their teacher as with their children, grandchildren or friends. This emotional investment would function as an internal motivation for them to pursue their goals disregarding practical difficulties or perceived inefficiencies. Moreover, depending on how each adult learner had experienced their formal tuition years, they might be faced again with feelings of overestimation concerning their knowledge and abilities, contempt, vanity, even despair in their attempt to master the FL. Resuming the role of the student at an elder age requires constant encouragement, respect, and support on behalf of the teacher because older adults seem to easily opt out of any activity which may be perceived as threatening. On the other hand, the presence of peers who are in a similar situation may be relieving or may arouse even more intense feelings of anxiety and withdrawal, when comparison comes to prominence. Despite any positive or negative feelings, however, the very act of walking into the FL classroom would definitely be regarded as a socially meaningful rejuvenating event, which would be accentuated by the enjoyment of starting to understand and timidly use the target language.

Because MCI older adults are too among Prensky's "digital immigrants" [2001], it would be challenging to teach them an FL using the affordances of technology. These learners should be somewhat digitally literate or in the process of learning how to use digital devices. The necessary presence of the teacher would be catered for with video-conferences. The teacher thus would be virtually close to the students, in order to deliver the lesson in almost the same way as in the classroom, and all participants would enjoy the comfort of a more relaxed setting. However, it might prove hard to overcome technicalities while, for the teacher, it would be difficult to intervene and provide immediate and corrective feedback. Nonetheless, a digital device is a very powerful seductive means and, in the FL case, it would engage the older adults in a double learning process: simultaneous computer and FL use. The lesson would acquire new attire, modern and youthful, unprecedented for these people who were only taught in the traditional classroom, which might now seem outdated.

On the other hand, leaving MCI older adults in the chaos of the Internet without any kind of guidance through the FL acquisition would seem an implausible venture. Considering that the majority of these people require more time to accomplish any set task, they would have to consume themselves in front of the computer screen, lost in the web, often to no avail. Such an attempt would not but hinder their willingness to learn the FL and expose them to a hostile environment which is not

older adult friendly. Bearing in mind that they form part of a population particularly vulnerable psychologically-wise, they might easily be discouraged and feel hopeless. Nonetheless, there would always be venturers who, because of growing familiar with the digital era and dare to put themselves to the test, would eagerly attempt to engage in the FL quest, just like young people. Presumably, the results would be highly remarkable and the whole process utterly rewarding, both in terms of cognitive reserve and FL learning.

Conclusion

FL education in the 21st century is sure to have dramatically evolved. New trends, novel possibilities, roads not taken lie ahead, largely due to the technological advancement. The typical student has become language user. The community of the class has opened up to engulf friends and peers from around the world. The rules, traditionally set by the teacher, emerge from the community. The activities are self-organised and the tools employed are individually chosen resources on personal equipment [Sockett, 2014]. The digital era in the FL education may be challenging long-established settings and the traditional role of the teacher, but neither is disregarded or dismissed. It is as though a classical theatrical play is being staged through the radically innovative perspective of a new director. It might inflict new beliefs on a very familiar topic. Yet, a new world is being created on the solid basis of what has been experienced for years. Everyone wishing to be an active part of it should adapt to the call of this new world, in order to allow it to flourish and be used for purposes beyond the original or typically expected scope.

All authors declare that they have no conflicts of interest

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Tsallis q-triplet and neurodegenerative diseases

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Abstract

This study presents results obtained from the statistical analysis of data of three neurodegenerative diseases, namely Amyotrophic Lateral Sclerosis (ALS), Parkinson's Disease (PD) and Huntington's Disease (HD). In particular, the data are comprised of time series corresponding to stride intervals (gait dynamics) for the ALS, PD, HD diseases and a healthy control. The statistical analysis is based on the estimation of Tsallis' q-triplet, namely $\{q_{stat}, q_{sens}, q_{rel}\}$. For all time series considered, evidence for non-Gaussian statistics and long range dependencies was found, since the results revealed significant deviation of Tsallis q-triplet from unity. Furthermore, nontrivial differences between ALS, PD, HD subjects from the corresponding healthy control subject. The results indicate that Tsallis statistics can be used for the development of possible biomarkers, as well as for gaining new insights into gait complex dynamics of the aforementioned neurodegenerative diseases.

Keywords: Neurodegenerative diseases -Tsallis q-triplet - Gait dynamics

Introduction

Neurological disorders consist one of the majors public health problems [WHO, 2006]. They are the cause of progressive nervous system dysfunction, afflicting the nervous system resulting in atrophy of the affected central or peripheral structures of the nervous system. Three paradigms of these diseases are: a) Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's Disease), which is generated by the destruction of motoneurons of cerebral cortex, brain stem and spinal cord, b) Huntington's Disease (HD) which is caused by the mutation of Huntington's gene and c) Parkinson's Disease (PD) which is caused by the malfunction of neurotransmitter called dopamine that transports signals to the parts of the brain that control movement initiation and coordination. All these diseases affect the human movement creating serious gait abnormalities, characterized by loss or dysfunction of neurons in motor, sensory, or cognitive system [Aziz and Arif, 2002 and refs. therein].

One way to study the aforementioned diseases is to analyze time series related to temporal gait parameters (e.g. stride, stance or swing intervals) which can provide information of the mechanisms of movement disorders [Zeng and Wang, 2015]. For example, human gait exhibits (multi)-fractal dynamics, while gait signals are characterized by aperiodicity, non-linearity and non-stationarity [Walleczek, 2000; Hausdorff et al., 2001; Goldberger et al., 2002; Stam, 2005; Delignières and Torre, 2009].

In this paper, we analyze gait time series using statistical analysis based on Tsallis non-extensive

statistical mechanics [Tsallis, 2009] and in particular, Tsallis *q*-triplet [Tsallis, 2004], which can provide significant information for the non-Gaussian statistical features of the gait time series. In particular, Tsallis [Tsallis, 2009] developed a consistent and effective theoretical framework, named non-extensive statistical thermodynamics which is based on a generalization of Boltzmann – Gibbs (BG) entropy, given by the relation

$$S_q = k\frac{1-\sum_{i=1}^{W} p_i^q}{q-1} \quad (q \in \mathbb{R}, S_1 = S_{BG}), \qquad (1)$$

where *k* is the Boltzmann's constant, *W* a set of discrete states and the *q* is the degree of nonextensivity. The Tsallis entropy S_q measures the complexity of the system, while the parameter *q* measures the degree of nonextensivity of the system. For example, for two probabilistically independent systems A and B, Eq. (1) becomes

$$S_q(A+B) = S_q(A) + S_q(B) + (1-q)S_q(A)S_q(B). \qquad (2)$$

The first part of Eq. (2) is additive while the second part is multiplicative, describing the long range interactions between the two systems. For $q > 1$ and $q < 1$ Eq. (2) holds for sub-additivity and super-additivity, respectively [14]. When *q* = 1, Eq. (2) corresponds to the entropy of the usual BG statistical mechanics, which is additive.

Tsallis *q*-indices can describe features of the dynamics of the complex system in study, such as sensitivity to the initial conditions, relaxation towards equilibrium of correlation functions, equilibrium distribution of energies, entropy production etc. Here, we are interested in indices $q_{\text{sensitivity}}$, $q_{\text{relaxation}}$, $q_{\text{stationary}}$, known also as Tsallis *q*-triplet [Tsallis, 2004], which constitutes also the best empirical quantifier of non-extensivity. In the following we describe briefly the underlying mathematical framework concerning Tsallis *q*-triplet [for an extensive review see Pavlos et al., 2014]:

Tsallis q-sensitivity index (q_{sen}): According to [Lyra and Tsallis, 1998] the power-law sensitivity to initial conditions at the edge of chaos provides a natural link between the entropic index *q* and the attractor's multifractal or singularity spectrum *f*(*a*). Therefore, we can use the multifractal spectrum in order to determine the entropic index q_{sen} which is given by

$$q_{sen} = 1 - \frac{a_{\max} a_{\min}}{a_{\max} - a_{\min}}. \qquad (3)$$

The $a_{\max}, a_{\min}$ values correspond to the extremes of multifractal spectrum for which $f(a) = 0$.

Tsallis *q*-relaxation index (q_{rel}): This index is given by $q_{rel} = (b-1)/b$, where *b* is the slope of the log-log plotting of auto-mutual information I_{KK_τ} given in [Fraser and Swinney, 1986] by the relation:

$$I = \sum_{x(t),x(t+\tau)} p(x(t), x(t+\tau)) \log_2 \frac{p(x(t), x(t+\tau))}{p(x(t))\, p(x(t+\tau))}, \qquad (4)$$

Auto-mutual information provides information gained about one measurement of atime series from the measurement of another. If the two measurements are completely independent, the auto-mutual information is zero.

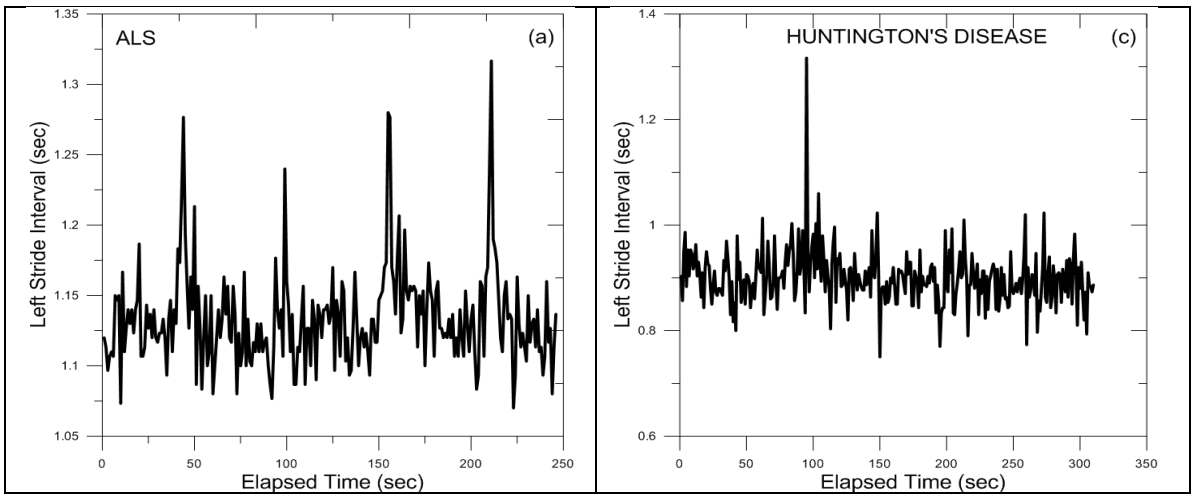
Tsallis q-stationary (q_{stat}): This index is connected with heavy-tail distributions, named Tsallis q-Gaussian distributions. The estimation of Tsallis q index, referred to as stationary $q=q_{stat}$, is related to the size of these distributions tail and can describe metastable stationary states of the system. The Tsallis q-Gaussian distribution [Umarov et al., 2008] is given by

$$G_q(\beta;x)=\frac{\sqrt{\beta}}{C_q}e_q^{-\beta x^2}, \qquad (5)$$

where $e_q=[1+(1-q)x]^{1/(1-q)}$ is the q-exponential, β is a positive number and C_q is a normalization constant, namely $C_q=\int_{-\infty}^{\infty}e_q^{-x^2}dx$. Depending on the q value, C_q has different forms [Umarov et al., 2008].

Results

In this paragraph, we present results concerning the analysis of gait dynamics of ALS, HD and PD diseases, while we also studied a healthy control for comparison [Hausdorff et al., 1997, 2000]. The time series analyzed (stride-to-stride measures of footfall contact times, and correspond to left and right stride intervals (sec)) are constructed from the records of the Physionet's database (http://physionet.org/physiobank/database/gaitndd/). In Figures 4a-f only the left strides are shown, while the right strides have similar profile. As the plots show, the stride intervals are irregular and non-periodic.



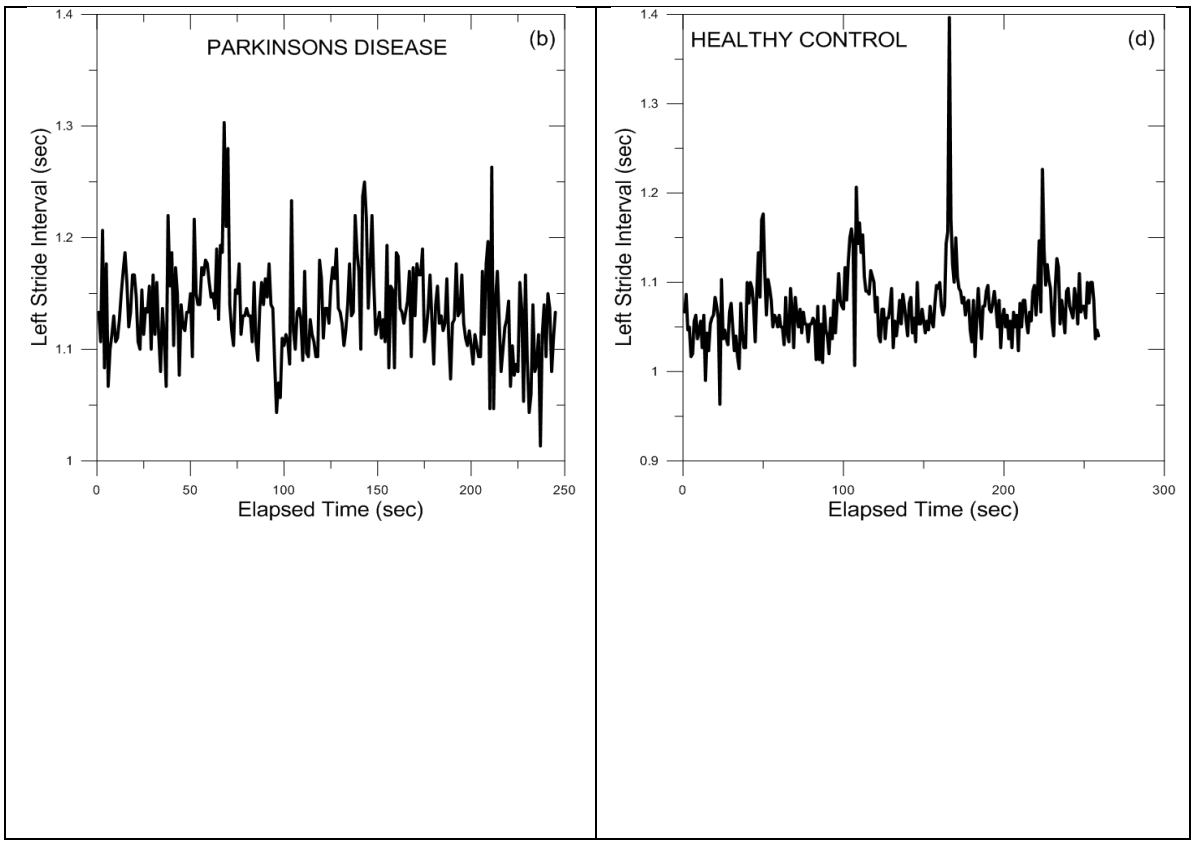


Figure 1. Examples of gait time series concerning left stride intervals (sec) of: **(a)** ALS. **(b)** Parkinsons. **(c)** Huntingons. **(d)** Healthy control.

ALS

The time series analyzed, consisting of 245 strides, corresponds to a female subject of age 40 years, height 1.7 meters and weight 61.24 kg. The results concerning the time series of left strides, are shown in Figure 2. In particular, in Figures 2a,d we show the results concerning the estimation of singularity spectrum $f(a)$ along with error bars and consequently for Tsallis q_{sen} index (as described in introduction). As it is shown, the time series has multifractal characteristics, denoting an intense complex self-similar character which manifests in many scales. In this case, q_{sen} is estimated equal to 0.1945 ± 0.015. In Figure 2b we present results concerning the Tsallis q_{rel} index. In particular, the best log $I(\tau)$ vs log(τ) fitting of the auto-mutual information function for the time series is presented. With the red dashed lines the power law fitting is shown, while with the blue dashed line the exponential fitting is emphasized. For a classical BG-process the mutual information should decay in exponential fashion. However, for the time series we do not find such behavior. In particular, the mutual information decays in a q-exponential manner (power law) for lags τ = 1-10, with a coefficient of determination for the power law fitting (R-squared) $R^2 > 0.92$ greater than the corresponding coefficient of exponential fitting. Therefore, using the slope b of the power law fitting we estimate q_{rel} index, as described in introduction, which was found to be $q_{rel} > 1$, namely $q_{rel} = 4.24 \pm 0.22$, indicating similar q_{rel}-exponential decay relaxation times to meta-equilibrium non-extensive stationary states for the time series. Finally, we also estimated Tsallis q_{stat} index for the time series. In Fig. 2c, we present the results concerning Tsallis q-Gaussians depicted by the solid red line in a log[$p(x_i)$] vs

x_i graph. In the same Fig. the Gaussian *PDF* (green line) is also shown. The difference in long tails is clearly pictured. The open blue circles correspond to the left stride interval time series. The Tsallis *q*-Gaussian corresponds to the best linear correlation between $\ln_q[p(x_i)]$ and $(x)_i^2$ (not shown here) and the Tsallis q_{stat} index was found above unity and particularly $q_{stat} = 1.22 \pm 0.06$, and the corresponding correlation coefficient (*cc*) is: 0.927 ± 0.01. This value of Tsallis q_{stat} index indicates that the presence of long-range interactions, characterized by non-Gaussian (*q*-Gaussian) distributions.

In Table 1 results are shown concerning both left and right stride intervals time series, along with the fitting parameters. In particular, Tsallis *q*-triplet was found $\{q_{sens}; q_{rel}; q_{stat}\} = \{0.1945; 4.24; 1.22\}$ for left stride intervals and $\{q_{sens}; q_{rel}; q_{stat}\} = \{0.113; 4.16; 1.78\}$ for right strides. Therefore, in both cases, the indices attained values different from unity denoting non-Gaussian statistics described efficiently by Tsallis non-extensive statistics. In addition, the Tsallis q_{stat} index is higher for right stride intervals indicating a possible asymmetry in the subject's movement and especially more correlated right strides.

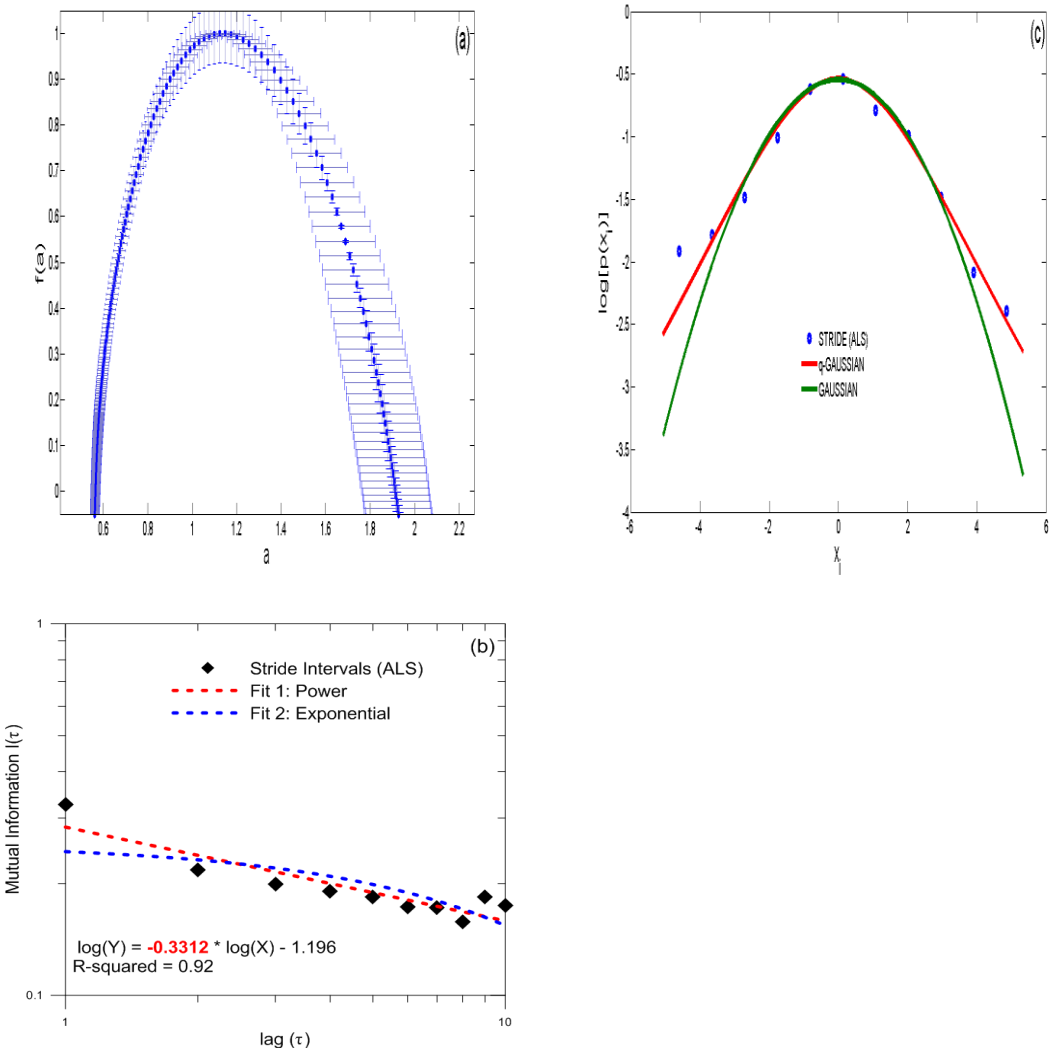


Figure 2: a) The singularity spectra *f (α)* as a function of singularity strength *α* for the ALS stride

intervals. b) Double logarithmic plot of auto-mutual Information $I(\tau)$ vs τ. for the ALS stride intervals. c) $\log(p(x_i))$ vs x_i graph for the ALS stride intervals.

Table 1. *Tsallis q-triplet for stride intervals corresponding to a female subject with ALS.*

Stride Interval (sec)	q_{stat}	q_{sen}	q_{rel}
Left	1.22 ± 0.06 *cc* =0.927±0.01	0.1945 ± 0.015	4.24±0.22 R^2 = 0.92±0.08
Right	1.78 ± 0.23 *cc* = 0.95±0.02	0.113 ± 0.05	4.16±0.6 R^2 = 0.89±0.05

Parkinson's Disease

The time series analyzed in this case, consisting of 245 strides, corresponds to a male subject of age 77 years, height 2 meters and weight 86 kg. The statistics were estimated in a similar way as presented in the previous paragraph. The results are presented in Table 2 along with the fitting parameters. Particularly, Tsallis q-triplet was found $\{q_{sens}; q_{rel}; q_{stat}\} = \{0.18; 3.76; 1.6\}$ for left stride intervals and $\{q_{sens}; q_{rel}; q_{stat}\} = \{0.352; 2.32; 1.395\}$ for the right stride intervals. Even though, in both cases, the indices attained values different from unity denoting non-Gaussian statistics which can be described faitfully within Tsallis non-extensive statistics, the Tsallis indices values are different for left and right stride intervals indicating a possible asymmetry in the subject's movement.

Table 2. Tsallis q-triplet for stride intervals corresponding to a male subject with Parkinson's Disease.

Stride Interval (sec)	q_{stat}	q_{sen}	q_{rel}
Left	1.6 ± 0.12, *cc*=0.95±0.04	0.182 ± 0.0577	3.7565 ± 0.244 R^2 = 0.773±0.07
Right	1.395 ± 0.055, *cc*=0.815 ± 0.015	0.352 ± 0.02	2.32 ± 0.04 R^2 = 0.738±0.18

Huntington's disease

For studying Huntington's gait dynamics a data set, consisting of 310 stride intervals, of a male subject of age 42 years, height 1.86 meters and weight 72 kg, was selected. The results are showed in Table 3 along with fitting parameters. Tsallis q-triplet was found $\{q_{sens}; q_{rel}; q_{stat}\} = \{0.613; 2.3; 0.8625\}$ for left stride intervals and $\{q_{sens}; q_{rel}; q_{stat}\} = \{0.226; 3.253; 1.385\}$ for the right intervals. Even though, in both cases, the indices attained values different from unity denoting non-Gaussian, non-extensive Tsallis statistics,

the Tsallis indices are significantly different for left and right stride intervals indicating strong asymmetry in the subject's movement resulting unsteady-jerky gaits. This can be clearly seen in Tsallis q_{stat} index since for left strides time series attains values below unity, while for right stride time series is above unity.

Table 3. Tsallis *q*-triplet for stride intervals corresponding to a male subject with Huntington's Disease.

Stride Interval (sec)	q_{stat}	q_{sen}	q_{rel}
Left	0.8625 ± 0.017, $cc = 0.915 \pm 0.01$	0.613 ± 0.0106	2.3 ± 0.2 R^2 = 0.836±0.11
Right	1.385 ± 0.2, $cc = 0.9586 \pm 0.044$	0.226 ± 0.013	3.253 ± 0.25 R^2 = 0.838±0.14

Healthy Control

Finally, for comparison, we also estimated Tsallis q-triplet for a stride intervals time series for a healthy control. In this case, the subject was a female of age 57 years, height 1.94 meters and weight 95 kg. The time series consists of 259 stride intervals. The results are presented in Table 4 along with fitting parameters. In particular, Tsallis *q*-triplet was found $\{q_{sens}; q_{rel}; q_{stat}\} = \{0.487; 3.146; 2.2\}$ for left stride intervals and $\{q_{sens}; q_{rel}; q_{stat}\} = \{0.49; 3.392; 2.04\}$ for the right intervals. In both cases, the indices attained values different from unity denoting non-Gaussian, Tsallis non-extensive statistics. In addition, the Tsallis indices values are very similar for left and right stride intervals, indicating strong symmetry and in the subject's movement resulting steady-correlated gaits, as expected from a healthy person. This result is in contrast with the previous results concerning the subjects with diseases which were characterized by asymmetry and uncorrelated gaits.

Table 4. Tsallis *q*-triplet for stride intervals corresponding to a healthy female subject.

Stride Interval (sec)	q_{stat}	q_{sen}	q_{rel}
Left	2.2 ± 0.37, *cc*= 0.73 ± 0.07	0.487 ± 0.025	3.146 ± 0.6 R^2 = 0.843±0.08
Right	2.04 ± 0.38, *cc*= 0.79 ± 0.05	0.49 ± 0.01	3.392 ± 0.95 R^2 = 0.78±0.15

Summary and Conclusions

In this paper, we analyzed statistical features of stride interval time series concerning neurodegenerative diseases, namely ALS, Parkinson's and Huntington's diseases. We also studied stride intervals of a healthy control for comparison. The methodology was based on Tsallis non-extensive statistics and in particular on Tsallis q-triplet. In particular, we showed that in all cases Tsallis q-triplet was found different from unity in all cases indicating non-extensive, non-Gaussian dynamics, indicating that the temporal fluctuations in the stride interval are not random but there is hidden information connected with Tsallis q-Gaussians distributions, characterized by the presence of long-range dependence. However:

ALS: Differences in the Tsallis q_{stat} index were found concerning left and right stride intervals indicate possible weak asymmetry in the subject's movement, which could be due to weakness, fatigue, loss of balance and coordination of the subject.

Parkinson's disease: Differences were found in all Tsallis indices concerning left and right stride intervals indicating an asymmetry in the subject's movement, a result which is in accordance with the Parkinsonian gait dynamics, which is characterized by small shuffling steps and a general slowness of movement.

Huntington's disease: A very significant difference was found concerning Tsallis q_{stat} index. In particular, Tsallis q_{stat} index for left strides is below unity, while for right strides is above unity. In addition, the other Tsallis indices are also different. These results indicate a strong asymmetry in the subject's movement resulting in from uncoordinated, unsteady-jerky gaits.

Healthy Control: All indices were found similar for left and right stride intervals, a result which indicates strong symmetry in the subject's movement resulting steady-correlated gaits, as expected from a healthy person.

Therefore the aforementioned results can provide valuable information, indicating different effects of each disease on gait asymmetry and nonlinearity on stride dynamics, changing with each disease providing new insights in disease severity, medication utility and fall in order to improve therapeutic interventions. These results are also in accordance with [Hausdorff et al., 2001; Hausdorff, 2007] who found fractal correlations in gait dynamics.

Finally, the estimation of Tsallis q-triplet could also be helpful for the discrimination of different types of epileptic seizures [Iliopoulos et al., 2016] and/or provide valuable information concerning EEGs of other neurodegenerative disorders, such as the Alzheimer's disease. Moreover, Tsallis statistics could help to clarify the differences and the similarities between the gait dynamics of the same disease as well as between the diseases, since the temporal fluctuations in the stride interval change with age and disease [Delignières and Torre, 2009]. In addition, other time series corresponding to sub-phases of the stride (e.g., stance and swing) could be examined and of course, in order to draw safer conclusions more subjects, both with disease and healthy, should be examined.

Acknowledgments

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All authors declare that they have no conflicts of interest

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Development and testing of a monitoring system assisting patients with mild cognitive impairment (MCI) using new technologies in the frame of the European project INLIFE

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Abstract

INLIFE is a European project cofounded by the European Union aiming in prolonging independent living of elderly people with cognitive impairment based on open, seamless services supporting communication, daily activities, providing health services and professional care to the elderly. The main INLIFE innovation stems from technology solutions offering 19 different services adapted on specific characteristics of user groups, like groups of elderly people with mild cognitive impairment, early and later stages of Dementia, cognitive impairment and co-morbid condition, as well as formal and informal caregivers.

The INLIFE project includes an infrastructure offering services with different focus areas, incorporated into a unified system based on cloud architecture implemented in patients of 6 European countries. More than 1200 patients, caregivers and healthcare providers are going to participate in the pilot testing of the project.

Primary parameter for assessing the effectiveness of the interventions is their impact on the quality of life of elderly patients and their caregivers contributing to prolonging independent living of the patients.

In the Greek pilot site a digital platform has been developed in order to adapt and monitor all the implemented applications. A specialized medical decision support system was also created, based on receiving biosignals from patients and interaction interfaces in which all participants are involved.

Recruitment and participation of patients has already started in the pilot site of Thessaloniki for the services that will be tested in Greece.

Keywords: New technologies - Cognitive impairment - Independent living - Assisted living - Healthcare monitoring

Introduction

The percentage of elderly people with cognitive impairment living autonomously depends on the different kind of underlying impairment [1]. INLIFE is a European project cofounded by the European Union aiming in prolonging independent living of elderly people with cognitive impairment based on open, seamless Informatics and Computer Technology (ICT) services supporting communication, daily activities, providing health services and professional care to the elderly. The main INLIFE innovation stems from ICT solutions offering 19 different services adapted on specific characteristics

of user groups, like groups of elderly people with MCI, early and later stages of Dementia, cognitive impairment and co-morbid condition, as well as formal and informal caregivers.

During the last years, services have been developed 'in parallel' with the needs and capabilities of users. Adopting technology is known to be very important for self-efficacy of people with dementia. Many ICT solutions have been proposed either for assessment of the Dementia burden or the assisted living of the affected persons: Automated speech analysis and video recording analysis can reveal critical information about the disease progression; computer memory games (serious games) may be useful tools in screening of cognitive decline; actigraphy has been proposed as an evaluation method in various disorders, including dementia [2].

The major challenge is providing a holistic service that can address all aspects of a person's life and the drawbacks posed by cognitive impairment (including challenges such as ICT literacy and non-adopters in the elderly population) [3, 4]. INLIFE project provides solutions to address these issues. It includes an ecosystem of infrastructures offering services such as: daily routine digital assistant, daily activity monitoring, brain exercise, memory improvement, fall detector, driving assessment, route planning support, e-doorbell, public transport usage support, socialization and communication, caregiving monitoring, patient management, teleconsultation, exercise assistant, distance medical intervention and formal carers' support [5-18].

Methods - Subjects

All services have different focus areas and are incorporated into a unified system based on cloud architecture implemented in patients of 6 European countries, including Greece, UK, Ireland, Sweden, Spain, Slovenia and the Netherlands. More than 1200 patients, 600 caregivers, 300 healthcare providers and 60 stakeholders are going to participate in the pilot testing of the project, with different levels of Activities of Daily Living (ADL) being tested in different pilot sites. In general, UK and Sweden will focus on testing applications targeting people with severe dementia or Alzheimer's Disease, whereas the rest of the countries will recruit patients and various stages of cognitive impairment. In Greece, the recruited patients fall into the category of mild to moderate cognitive impairment with or without other comorbidities, like Chronic Obstructive Pulmonary Disease (COPD), Congestive Heart Failure (CHF), Diabetes Mellitus, Hematologic Malignancies and Orthopedic Surgical Conditions.

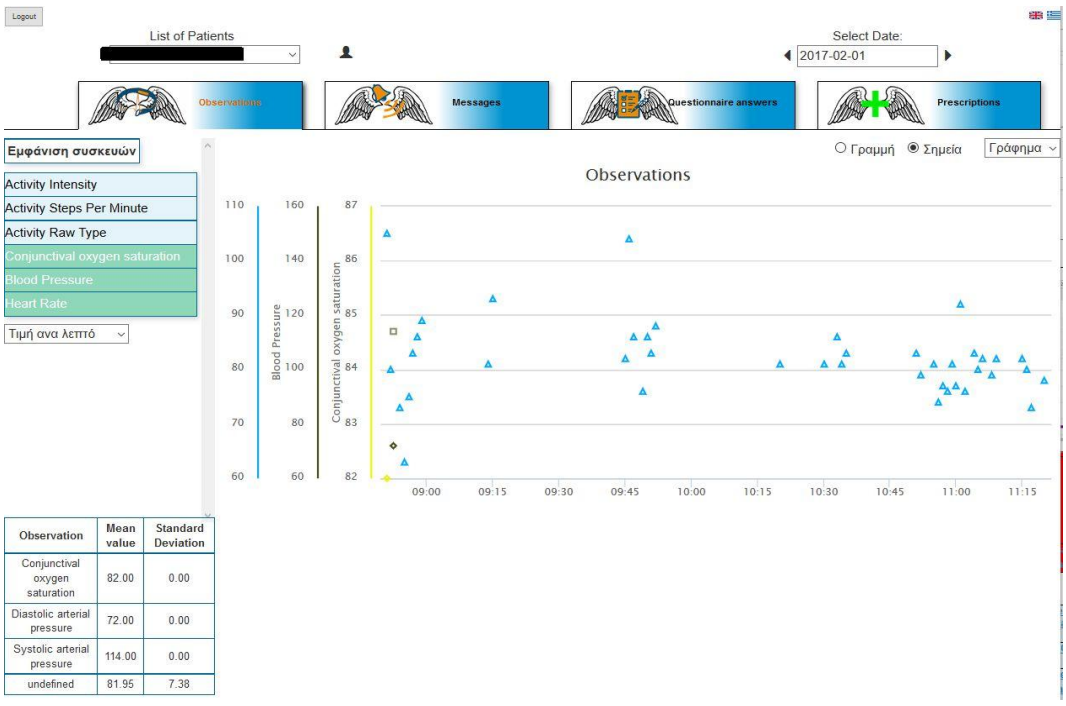
Primary parameter for assessing the effectiveness of the aforementioned interventions is their impact on the quality of life of the elderly patients and their caregivers contributing to prolonging independent living of the patients [4, 10]. The endpoints will be assessed using validated questionnaires administered to the test subjects at the beginning and the end of the pilot phase of the study. Comparisons will be made between the before and after the intervention states, as well as between the intervention and the baseline assessment phase. The latter was performed using an equal number of matched subjects without the use of any proposed intervention, mirroring the current state of healthcare provision in these cases.

A special digital platform has been developed in the Greek pilot site in order to adapt and monitor all the applications implemented in the interventions. In addition, a specialized medical decision support system was created, based on receiving bio-signals from patients and interaction interfaces in which all participants are involved.

condition	condition	condition	condition	condition		outcome/action
Current Diseases contains J44*	Current Diseases contains F30*-F39*	Total Resting Activity > 120% baseline	Deviation from baseline Spo2 resting<3	Deviation from baseline HR resting<15%		1.Send motivational message to patient/carer 2. Inform pulmonologist & psychiatrist
Current Diseases contains I50*	Deviation from baseline HR resting >15%	Deviation from baseline Spo2 resting <= -3	Ankles Swollen (question 4 = YES)	Deviation mMMRC from previous >0		1. Possible Acute Pulmonary Oedema 2. Visit Emergency Room 3. Alert Cardiologist/Pulmonologist

Figure 1. Examples of complex rules for the Medical Decision Support System for the InLIfe project. J44=COPD, I50=CHF, F30-39=Anxiety and Depression Disorders, mMRC=validated dyspnea scale.

Recruitment and participation of patients has already started in the pilot site of Thessaloniki for the services that are to be tested in Greece. Guardian Angel is a telemonitoring platform that consists of a wristband as a wearable device coupled with a tablet and right now they are both- literally - in the hands of most INLIFE participants. Through a digital platform (called Application Centre) end-users' health status can be measured during their daily routine. Monitoring the collected data sent to the platform through the wristband's special sensor, means transferring information regarding the basics, such as heart rate, blood pressure, daily steps, hours of sleep. Healthcare professionals and informal carers can have access to the collected data. Through a smart Decision Support System, the application provides alerts, warnings and motivation messages to the user and to the informal caregiver. Guardian Angel is a precious assistant for healthcare professionals while providing information in detail regarding the health status of the patient.



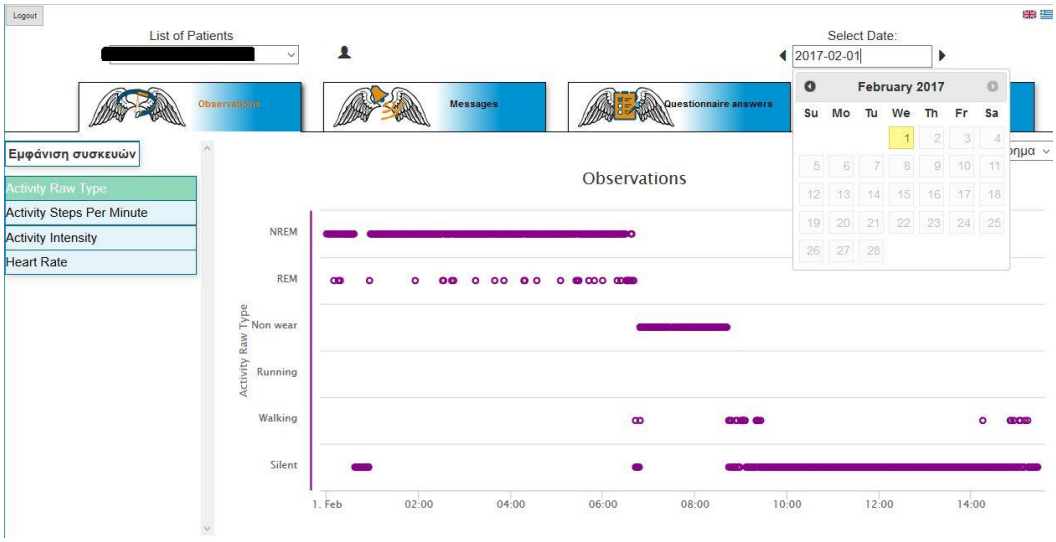


Figure 2. Screenshots of the healthcare professional Interface for the monitoring of vital parameters in the InLife platform.

INLIFE's project second phase also includes giving out oximeters and blood pressure monitors to certain patients according to their health status, thus providing enhanced monitoring capabilities to the attending physicians. The patients may also fill disease specific questionnaires and engage into carefully designed serious games via their tablet devices, in order to exercise their memory and assess their attentive skills. The scope of services provided and the vital signs monitored are personalized depending on the underlying diseases in every patient. The memory support tools are intended for all the participating subjects.

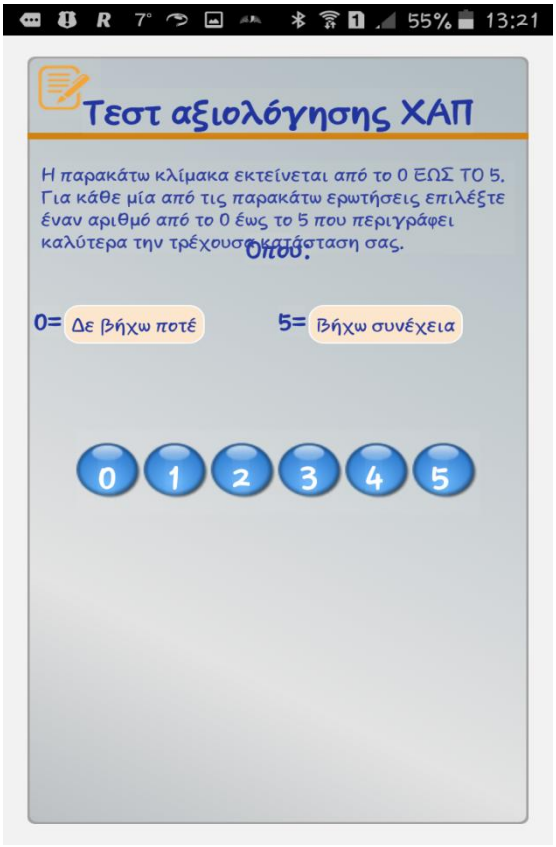


Figure 3. Screenshot of the tablet interface for a disease specific questionnaire (A simple Likert Scale for the frequency of cough episodes).

Finally, the Greek pilot site will evaluate the driving capability of active elderly drivers who often present with MCI. This will be achieved using an adapted computer based test battery situated at the Centre of Research and Technology in Thessaloniki, Greece [8, 9]. The test battery ranks the patients into categories depending on their ability to drive safely, which is evaluated in three stages. The tests are followed by real life driving assessment with an accompanying driving instructor using a specially adapted car in doubtful cases.

Expected Results

Different indices will be assessed in different countries and different applications, according to the main target of each solution. However, common evaluation items will be the health-related quality of life, the user satisfaction from the provided technologies, the patients' independent living status and mental state as well as the burden of their care for their carers. The healthcare professionals and the local stakeholders will also provide feedback on the usability, value and applicability of the INLIFE concept as a holistic patient-centered approach. Preliminary results from the Greek pilot dictate that the system is well accepted by the majority of the users, it is considered of high value by the healthcare professionals and the carers, whereas the vital signs obtained by the relevant applications are indicative of the health status of the affected patients. The validity of the medical decision support system is currently under evaluation and the final questionnaires indicating various aspects of the patients' independent living will be filled at the end of the pilot phase during this summer.

Discussion

The INLIFE Project is an ambitious research endeavor aiming to highlight the needs of elderly people with cognitive impairment at a pan-European level as well as evaluate existing ICT interventions that could be able to assist these patients in the frame of independent living and quality of life. Its strong points are the high diversity of the proposed ICT solutions, the integration of the services under a common configurable platform, its personalized approach and finally, the large number of participants from different European countries. Different healthcare systems can be served through the centralized approach of the INLIFE platform and various players in the field of healthy aging will be addressed, since patients, formal and informal carers, stakeholders and healthcare professionals will be parts of the evaluation strategy during the project duration. In addition, patients with different stages of cognitive impairment will be assessed and best practices in the related fields will be established. The preliminary results show promising effects of the proposed interventions regarding the user satisfaction and the independent living of the participating subjects. These results must be reinforced and proven significant after the final evaluation of the interventions towards the end of the project in the near future.

All authors declare that they have no conflicts of interest.

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Driving practices in professional drivers with dementia

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Abstract

Overview: We identified 43 individuals over 65 years of age with a professional driving license and cognitive disorders from 153 tested for their driving ability. Similar studies in elderly professional drivers with dementia have not been found in the literature. The aim of our study was driving habits in elderly professionals drivers with Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI). **Method:** All (153 individuals) were outpatients of the 3rd University Department of Neurology of "G. Papanikolaou" General Hospital. Forty three of them answered 'Yes' (28.1%) and 110 (71.9%) 'No' in the question "Do you possess a professional driving license"? From the 153 individuals, 44 had MCI, 55 AD, and 54 were community dwelling older adults. The participants were tested through a neurological examination and neuropsychological and neuropsychiatric evaluations and lab exams for the confirmation of MCI and AD diagnosis. They were also tested for their driving ability through a questionnaire of 33 questions and 52 sub-questions. **Results:** Among AD individuals, most non-professional drivers did not renew their license compared with professional ones. Additionally, in the MCI group, most non professional drivers cover fewer kilometers in comparison with professionals. In the community dwelling older adults group, most professional drivers consider that they drive as well as they did in the past compared with the non-professionals. Furthermore, in the MCI and AD group, most non-professional drivers always avoid driving in unknown areas when compared with the professional ones. **Conclusions:** Individuals with cognitive impairment and previous professional experience, behave better during driving compared with those without such experience.

Keywords: Dementia – Driving - Professionals drivers - Occupational Therapy - Alzheimer disease.

Introduction

Alzheimer's disease (AD) is characterized by a phased and progressive decline of cognitive functions. The succession of deficits usually relates to memory, language and visuo-spatial functions [1]. As the population continues to increase, the number of individuals suffering from dementia is estimated to reach 135 million until 2050 [2]. In the U.S.A. 5.2 millions suffer from dementia, of whom 200.000 are under the age of 65. In Greece it is estimated that 150-200.000 suffer from the disease. Today, every 3 seconds dementia is developed in one individual [3].

Driving in old age is associated with health and independence. With the increasing number of the elderly, their safe transportation becomes a worldwide problem [4]. In the U.S.A. 31 million elderly people above the age of 65 have received a driving license (National Service of Road Safety) [5]. The demographic data support that the existing policies for transportation programs should be renewed so as to support the participation of elderly drivers and to reduce the associated injuries and deaths [6].

The elderly people's driving ability is inherently associated with their identity and wish to maintain their independence [7]. The loss of their driving license leads to a 'career of dependence', in which the individuals should rely on others for their transport [8]. For the individuals with AD the loss of driving privileges could be abrupt and traumatic [9]. The former drivers who lose their means of transport feel isolated and face deep distress [10]. A better understanding of the dynamic of the loss of driving should be developed for the change brought about in the way of transport and adjustment of the elderly [11].

Driving and transport belong to the category of the Instrumental Activities of Daily Living (IADL) [12], and constitute a sub-category of the range of transport functions [13] through public and private means [14]. The role of occupational therapy could facilitate the participation of the elderly in the community during their transport [15]. Driving is a Complex Task demanding the healthy function of many cognitive and functional abilities, if it is to be conducted without any risks both for the driver and others [16]. The driving ability of individuals with AD and Mild Cognitive Impairment (MCI) who were professional drivers has not been investigated yet.

AD affects driving ability. Although driving is an automated procedure concerning vehicle operation which is more connected with procedural memory is complex as far as the processing of environmental stimuli is concerned, since the patient should properly assess distances, handle many stimuli simultaneously, have focused attention while driving, react promptly to risk and interpret the Highway Code correctly [17]. In individuals with AD there is a confusion between the start and acceleration pedal with the brake, they do not drive maintaining the appropriate speed, do not observe traffic signs, may unnecessarily stop (for example, at a green light), do not take the right decisions (slow reaction), have particular difficulty in left turns, often cause damage to the car, have difficulties in getting the right direction (orientation difficulty) and other drivers often honk [18]. They also drive less frequently in remote towns, less during a typical week and take fewer passengers in comparison to the previous year [19].

The ethical issues related to AD and driving turn to the principle of non-harmfulness and concern driving with safety [20]. However, some drivers maintain their driving ability for a longer period [21],

which is considered to be related to their former profession, if for instance they were professional drivers. Additionally, in individuals with MCI, the self-assessment of driving skills is maintained and the patients themselves plan discontinuing driving [22].

There are available interventions (The American Occupational Therapy Association, Inc.)(AOTA)[23] through Evidence-Based Driver practices, which affect performance and the elderly participation for safe driving, as well as European programmes for the elderly and individuals with dementia (AGed people Integration, mobility, safety and quality of Live Enhancement through living) (AGILE) [24]. While for individuals with physical impairment modifications in the equipment of the vehicles could be made so as to facilitate their adjustment to driving, interventions for individual with cognitive and perceptual disorders are more difficult. Individuals with AD do not correspond to driving interventions and mainly focus on their smooth adjustment and planning of driving discontinuation [25] through medical and social health models [26].

Assessment of driving abilities (Driver-Assessor-Trained Occupational Therapists) (DATOTs) [27] is based on observing Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) as well as on the results of assessment batteries for recommendations to be made [28] or training interventions for driving skills to be applied [29]. In AD individuals at the early stages for cognitive impairment, the interest is also focused on safety, since the transport ability with orientation and protection of the individual in cases of situations which threaten their safety are assessed [30]. Assessing AD individuals' driving ability becomes a more and more frequent clinical problem [31]. A clinically appropriate method is the clinical examination and use of neuropsychological tests [32].

Neuropsychological tests are used to predict the safe driving behaviour and control [33]. Automated Neuropsychological Assessment Metrics (ANAM) [34] has been proven sensitive in cognitive disorders caused by medication side effects [35] and mild brain damages. Their relatively bad use in clinical practice to evaluate driving ability, though [36], is associated with the lack of driving behavior models [37]. Short-term memory, visual observation as well as the result in the Mini Mental State Examination (MMSE) [38] had higher correlations with driving ability. The type and extent of cognitive functioning is the best predictor of driving ability than age or diagnosis. However few studies have shown the prognostic validity of MMSE to assess performance in on-road testing [39]. The strongest prognostic indicator for driving discontinuation is the combination of caregivers' worry about the patient's driving with the patients' score in Clock-drawing Test [40], which represents 62% of the variance in the decision of driving discontinuation ($p=<0.01$) [41].

The driving simulator is use to assess driving ability in the elderly with neurological diseases [42, 43], but its use for individuals with AD has not yet been widely accepted, although it is a potentially useful tool for research [44]. In Greece there have been measurements in the driving simulator in individuals with AD and MCI at the Hellenic Institute of Transport (HIT), Centre for Research and Technology Hellas (CERTH) in Thessaloniki.

In addition, individuals with AD performed significantly lower than normals in the test on real road conditions (P-Drive) [45], while an important minority performed at an acceptable level [46]. Studies on the effectiveness of the test assessing the driving-related skills of people with AD have produced different results [47].

The aim of our study was driving habits in elderly professionals drivers with Alzheimer's Disease and Mild Cognitive Impairment.

Material and Method

Participants

Six hundred thirty nine (639) individuals in total were evaluated for their driving ability in the Outpatient Clinic for Memory and Dementia of the 3rd Neurological Clinic of 'G. Papanikolaou' Hospital of the Aristotle University of Thessaloniki, and in day centers for dementia in Athens and Thessaloniki from December, 2012 to September, 2016. One hundred fifty three (153) individuals over 65 years of age were selected, from whom 55 were diagnosed with AD, 44 with MCI and 54 with community dwelling older adults were healthy controls (HC). From the 153 participants, 43 had a professional driving license and 110 not. Participants of a younger age were excluded as well as those who suffered from dementia of a different etiology (Vascular dementia, Parkinson's disease, etc).

Diagnosis

The participants were diagnosed with AD, based on National Institute of Neurological and Communicative *Disorders* and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ARDRA) criteria [48], and with MCI according to Petersen and Winblad's criteria [2, 3] by a group of specialized health professionals. A neurological examination, neuropsychological and neuropsychiatric evaluations, neuroimaging and blood tests were conducted along with the acquisition of the medical/social history to support the diagnosis of AD and MCI.

For the disease to be confirmed based on the NINCDS-ARDRA criteria there should be histopathological findings for the disease either by autopsy or biopsy. For the suspected disease, there should be impairment of memory and in one more mental field, absence of impairment of consciousness, the onset of the disease to be between the ages 40 and 90 and absence of any other brain condition leading to dementia. Finally, to consider a possible disease atypia should be observed at the onset and the progression of the disease, and there should be another mental impairment and a pre-existing mental disorder.

Assessment

Two questionnaires were combined by the research team to produce a third one which was distributed to individuals with cognitive impairment.

The first one was the Driving Questionnaire for patients with dementia [49]. Its aim was to detect the factors that constitute indicators for driving discontinuation and to find correlations between the driving behaviour of patients at the early stages of the disease and their mental condition. The questionnaire includes 40 questions, concerning the year of the driving license acquisition, the type of the license, the conditions under which the patient drives, the accidents they caused and the conditions under which they occurred, the number of vehicle changes so far, the influence of drugs on driving, the recommendations that the patients may have received by the doctor and their family environment for driving discontinuation, their personal perception about their driving behaviour and

other question. Its reliability and validity are good (Cronbach's alpha=.80) and it is distributed to the patients themselves by the clinician, with the presence of their caregivers for the confirmation of the information given by the patients.

The second questionnaire was the Aged People Integration, mobility, safety and quality of Live Enhancement through Living (AGILE) [50], which was adjusted for use for patients with dementia. The aim of AGILE was to develop new assessment procedures for driving and training methods for elderly drivers. Its basic concept was to allow to the elderly to continue driving a vehicle with safety for as long as possible, because driving as an individual way of transport have become almost a need for one to keep up with the current standards of mobility.

The new questionnaire included 33 questions with 52 sub-questions. More specifically, we asked information about the following subjects.

- Personal information: Sex, age, driving license details, accidents in the past, whether patients regard themselves good or bad drivers, etc.
- Views concerning training and assessment related with age: Whether they already had an evaluation associated with age, what they generally believe about the evaluation associated with age, whether they are willing to be retrained regarding their driving skills, how these assessments should be conducted, etc.
- Physical and mental skills: questions about the moving parts of the body, vision, hearing perception, vascular problems, attention, memory, etc.
- Driving habits: which traffic conditions they try to avoid, how they compare their driving today with when they were 45 years old.

All participants were examined with a battery of neuropsychological tests: Mini Mental State Examination - (MMSE) [51], Clock-drawing Test [40], Functional Rating Scale for Symptoms of Dementia (FRSSD) [52], Geriatric Depression Scale (GDS)[53], Hamilton's Depression Rating Scale (HDRS) [54, 55], and Functional-Cognitive Assessment Scale (FUCAS) [56, 57]. All these batteries were used as routine for AD and MCI staging. The healthy elderly were also examined with the same neuropsychological battery.

Statistical Analysis

The statistical analysis includes descriptive statistics and univariate analysis. Initially the normality of the distribution of the quantitative variables was tested by the Shapiro-Wilk test. In univariate analysis, comparing rates and consistency check between categorical (qualitative) variable, the x^2 test of independence was used. For the comparison between two independent quantitative measurements the statistical independent samples t-test was used where appropriate. The significances (p control values) less than 0.05 were considered statistically significant. The statistical analysis was performed with the statistical software SPSS v. 21.0.

Results

Demographic Characteristics

From 153 individuals 55 (35.9%) were diagnosed with AD, 44 (28.8%) with MCI and 54 (35.3%) were healthy elderly individuals (HC) as a control group. All participants were above 65 years of age. In total 119 (77.8%) men and 34 (22.2%) women were tested. In Greece there are very few women who drive at this age.

Their marital status is as a follows: 125 (81.7%) were married, 8 (5.2%) widowed, 2 (1.3%) single. Concerning their profession 143 (93.5%) were pensioners and 10 (6.5%) not. From 153 participants 43 (28.1%) answered Yes to the question whether they had a professional driving license and 110 (71.9%) replied negatively.

Table 1. *Demogrhaphic characteristics*

		Healthy Controls N(%): 54 (35.3%)	**MCI N(%):** 44 (28.8%)	**NA N(%): 55** (35.9%)	**Total N(%):** 153 (100%)	**p**
Age	«65-74»	30 (55.6%)	16 (36.4%)	17 (30.9%)	63 (41.2%)	0.085
	«75-84»	23 (42.6%)	25 (56.8%)	34 (61.8%)	82 (53.6%)	
	«>=85»	1 (1.9%)	3 (6.8%)	4 (7.3%)	8 (5.2%)	
Sex	Male	38 (70.4%)	33 (75.0%)	48 (87.3%)	119 (77.8%)	0.092
	Female	16 (29.6%)	11 (25.0%)	7 (12.7%)	34 (22.2%)	
Professional driver	No	42 (77.8%)	34 (77.3%)	34 (61.8%)	110 (71.9%)	0.115
	Yes	12 (22.2%)	10 (22.7%)	21 (38.2%)	43 (28.1%)	

The individuals in the healthy group have significantly more years of education compared to the rest (p=0.003). Also, the healthy non professional drivers have proportionally more years of education compared with the professional ones (p=0.012). Professional drivers have significantly fewer years of education (8.93±4.88) compared to the non-professional (11.77±5.26) (p=0.003).

There is no significant difference in MMSE between professional and non-professional drivers (p=0.751).

In all three diagnostic categories there are no women drivers with a professional license, HC (p=0.011), MCI (p=0.038) and AD (p=0.026).

Views concerning training and assessment related with age and driving habits

There is dependence between two variables with regard to the diagnosis in the questions: For which type of vehicle your license is/was valid (motorcycle, passenger car, lorry, bus, special trailer). The healthy non-professional drivers with a license for a motorcycle are more than the professional ones (p=0.003). In all diagnostic categories more professional drivers have a license for a lorry in relation to non-professional ones, HC (p<0.001), MCI (p<0.001) and AD (p<0.001). In the HC and in AD individuals more professional drivers have a bus license in comparison with the non-professionals, HC (p<0.001), MCI (p=0.062) and AD (p<0.001). In the Healthy and AD individuals more professional drivers have a license for a special trailer in relation to the non-professionals, HC (p<0.001), MCI (p=0.062) and AD (p=0.008).

Regarding driving habits in AD individuals, more non-professional drivers have not renewed their license in comparison with the professional ones (p=0.048). In MCI individuals, more non-professional drivers cover fewer kilometers in proportion with the professionals (p=0.029). Moreover, more professional drivers with AD would rent a car in comparison with the non-professionals with AD (p=0.009). In the MCI individuals non-professional drivers were not the main family drivers in proportion with the professionals (p=0.038). In the HC more professionals regard that they drive as well as in the past than the non-professionals (p=0.008).

Table 2. *Driving habits*

DIAGNOSIS			**Professional drivers**		**Total**	**p**
			NO 110 (71.9%)	**YES** 43 (28.1%)	**N(%):** 153 (100%)	
Healthy Controls N(%): 54 (35.3%)		Yes	5 (12.8%)	1 (11.1%)	6 (12.5%)	0.889
		No	34 (87.2%)	8 (88.9%)	42 (87.5%)	
MCI **N(%): 44 (28.8%)**	**Do you cover the same kilometers as in the past?**	Yes	2 (8.3%)	3 (42.9%)	5 (16.1%)	0.029

		No	22	4	26	
			(91.7%)	(57.1%)	(83.9%)	0.639
NA N(%): 55 (35.9%)		Yes	3 (15.0%)	1 (9.1%)	4 (12.9%)	
		No	17(85.0%)	10(90.9%)	27(87.1%)	
Healthy Controls N(%): 54 (35.3%)		Yes	36 (92.3%)	10 (90.9%)	46 (92.0%)	0.880
		No	3 (7,7%)	1(9.1%)	4(8.0%)	
MCI N(%): 44 (28.8%)	**Have you renewed your driving license?**	Yes	27(81.8%)	10(100.0%)	37(86.0%)	0.146
		No	6 (18.2%)	0 (0.0%)	6 (14.0%)	
NA N(%): 55 (35.9%)		Yes	25 (78.1%)	17 (94.4%)	42 (84.0%)	0.048
		No	7 (21.9%)	0 (0.0%)	7 (14.0%)	
		I do not remember	0 (0.0%)	1 (5.6%)	1 (2.0%)	
Healthy Controls N(%): 54 (35.3%)		Yes	24 (57.1%)	9 (75.0%)	33 (61.1%)	0.263
	Are/were you the main family driver?	No	18 (42.9%)	3 (25.0%)	21 (38.9%)	

MCI **N(%): 44 (28.8%)**	Yes	23 (67.6%)	10 (100.0%)	33 (75.0%)	0.038
	No	11 (32.4%)	0 (0.0%)	11 (25.0%)	
NA **N(%): 55 (35.9%)**	Yes	24 (70.6%)	18 (85.7%)	42 (76.4%)	0.200
	No	10 (29.4%)	3 (14.3%)	13 (23.6%)	

Physical & mental ability

There is independence between the two variables with regard to the diagnosis in the questions: about the moving parts of the body, vision, hearing perception, vascular problems, attention, memory, various health problems, such as cardiological problems, diabetes, epilepsy, cataract, glaucoma, stroke, etc. The frequent change of the psychological state from day to day. The frequent change in the physical condition from day to day. Doctor's recommendation for driving discontinuation for a reason. In the AD individuals more professional drivers believe that a test for the physical condition should be conducted in relation to the non-professionals (p=0.023).

Avoidance of Driving

There is independence between the two variables concerning the diagnosis in the questions: Avoidance of short-distance routes (about 15 minutes), middle-distance routes (about 30 minutes), long-distance routes (about 45 minutes or more). Avoidance of driving in rural areas, during the night, when raining, and on icy roads. Avoidance of overtaking and reverse driving. Avoidance of driving when tired. Have you ever been lost while driving? Good preparation in advance of the routes to be followed. If yes, describe the method of preparation (preparing the vehicle, searching the routes in maps, asking friends or relatives, on-line search, other). More careful driving today than when 45 years old. The average safety distance from the other cars is longer today than when 45 years old.

In the MCI and AD groups more non-professional drivers always avoid driving in unknown areas than the professionals, MCI (p=0.045) and AD (p=0.026). Moreover, in the AD group more non-professionals avoid driving while snowing in relation the professionals (p=0.034).

Table 3. Avoidance of driving

DIAGNOSIS			Professional driver		Total	p
			NO 110 (71.9%)	YES 43 (28.1%)	N(%): 153 (100%)	
Healthy Controls N(%): 54 (35.3%)		Never	21 (56.8%)	9(81.8%)	30(62.5%)	0.146
		Sometimes	10 (27.0%)	0 (0.0%)	10(20.8%)	
		Always	6 (16.2%)	2 (18.2%)	8 (16.7%)	
MCI N(%): 44 (28.8%)	Avoidance of driving in unknown areas	Never	14(48.3%)	7(100.0%)	21(58.3%)	0.045
		Sometimes	7(24.1%)	0 (0.0%)	7 (19.4%)	
		Always	8(27.6%)	0(0.0%)	8 (22.2%)	0.026
NA N(%): 55 (35.9%)		Never	3(15.8%)	7(58.3%)	10(32.2%)	
		Sometimes	4(21.1%)	0(0.0%)	4 (12.9%)	
		Always	12(63.2%)	5(41.7%)	17 (54.8%)	0.825
Healthy Controls N(%): 54 (35.3%)		Never	11(28.9%)	4(36.4%)	15 (30.6%)	
		Sometimes	10(26.3%)	2(18.2%)	12 (24.5%)	
		Always	17(44.7%)	5(45.5%)	22 (44.9%)	0.316
MCI	Avoidance of driving	Never	6 (20.0%)	4 (44.4%)	10 (25.6%)	

N(%): 44 (28.8%)	while snowing					
		Sometimes	12(40.0%)	2(22.2%)	14 (35.9%)	
		Always	12 (40.0%)	3(33.3%)	15 (38.5%)	
NA N(%): 55 (35.9%)		Never	3(15.0%)	4(26.7%)	7 (20.0%)	0.034
		Sometimes	1(5.0%)	5(33.3%)	6 (17.1%)	
		Always	16(80.0%)	6(40.0%)	22 (62.9%)	

Discussion

In this study from the 153 participants, in the question whether they had a professional license 43 (28.1%) answered positively and 110 (71.9%) negatively. Similar studies among the elderly with AD and MCI who were professional drivers have not been found in the literature.

We used a driving questionnaire with 33 questions with 52 sub-questions. In particular, we asked for personal information and for the participants' views on subjects concerning training and assessment in relation to age, the physical and mental ability as well as their driving habits. A similar study but in healthy individuals has been conducted by Sommer et al [58]. They investigated 473 elderly drivers aged 55-64, 65-74, >74 years with regard to their driving habits, accidents, their compensating behaviour in driving, as well as their attitude regarding the reassessment of their driving license due to their age. There was an increase in the elderly percentages who mentioned that they had full liability in their last road accident.

In this study the results showed that in individuals with AD more professional drivers believe that there should be a reassessment of their physical conditions in relation to to the non-professionals (p=0.023). Some studies report that some drugs can improve driving skills (antidepressants, anti-inflammatory, and potentially beta blockers) [59], while other drugs pose risks – in the case of neuroleptics [60]. Driving ability testing should emphasize on the neurological, sensory and emotional skills to improve the individuals' general health, as well as on other relevant to driving conditions such as vision problems [61]. The total driving ability requires many elements to form an individualized assessment, bearing in mind that the elderly under assessment for driving have multiple morbidity (vision, hearing, spasms) [62].

The results of this study showed that in individuals with AD more non-professional drivers did not renew their driving license in comparison with the professionals (p=0.048). In a similar study it is mentioned that individuals with dementia, pre-dementia and with Parkinson's disease have

discontinued driving during the last five years more than individuals without any Central Nervous System (CNS) disorder [63]. Other authors also mentioned a correlation between dementia and driving discontinuation [64]. The risk associated with driving limitation was higher at the pre-dementia phase than in dementia which is due to the time between the diagnosis and insight. Some individuals with dementia are not part of the elderly population who drive, because they limit or discontinue driving while they are in the pre-dementia stage. The factors influencing driving limitation differ with regard to sex, a phenomenon particularly intense among women [65]. In another study the results were different showing that the groups did not vary between them in relation with the limitation of driving frequency during the last year (p=>0.05) or participants preferred not to drive or to limit driving under certain conditions (p=>0.05). The effect of cognitive disorders on self-reported driving condition, driving habits and intentions of driving discontinuation in the future was investigated. The 179 participants were classified in those who had cognitive impairment and not dementia (Cognitive Impairment Non Dementia CIND-single), CIND-multiple, and to those with no cognitive impairment (Non Cognitive Impairment NCI). The groups differed significantly regarding driving condition, but they did not differ concerning driving limitation or limitation of driving frequency. The CIND-multiple group had a significantly higher intention of limiting or discontinuing driving than the NCI group. Independent of the mental status, none of the drivers thought of limiting or discontinuing driving in the next 6 months [66].

Additionally, the results of this study showed that in MCI individuals more non-professional drivers cover fewer kilometers in proportion to the professionals (p=0.029). In another study, it is mentioned that the emphasis on reaction time (a meter which is an integral part of operational tasks) is wrong, because drivers of a younger age group (15-25 years of age) is the group with the higher percentage of accidents. Elderly drivers are known to widely use strategies and tactics to avoid driving risks, such as low speeds, avoidance of driving during rush hours, as well as unknown routes, etc [67]. The reported use of various compensatory strategies and adjustment tactics in driving habits is higher among the elderly [58].

In this study the results showed that in the HC more professional drivers consider that they drive as well as in the past in comparison with non-professionals (p=0.008). In another study, through video recording 18 individuals with AD and 20 healthy individuals were analyzed in order to test self-regulation of drivers' behaviour and to assess the behavioral change due to cognitive impairment. Individuals with AD limit their driving behaviour more than the healthy elderly. These data offer findings of vital significance, because they show an overall decrease in driving of elderly drivers with cognitive impairment [68].

Regarding risk avoidance during driving, the results showed that in AD individuals more non-professional drivers avoid driving while snowing in relation to the professionals (p=0.034). Furthermore, in individuals with MCI and AD more non-professional drivers always avoid driving in unknown areas in comparison with the professionals, MCI (p=0.045) and AD (p=0.026). Likewise, in another study among patients with AD and Parkinson's disease it was found that there are no different patterns regarding reduction in driving safety in all domains than the healthy individuals. Significant findings showed that all cognitive domains, including information processing speed, visuo-spatial ability, speed and memory, predicted different aspects of older driver on road risks for safe driving more than age, visuo-spatial function and disease status [69].

In connection with vehicles, the results showed that the HC non professionals with a license for a

motorcycle are more than the professionals (p=0.003). Proportionally, more professional drivers with AD would rent a car in relation to non-professionals with AD (p=0.009). Applying the principles of universal design for the design of vehicle safety features is recommended as a strategy to enhance the possibility of their use by people with a broader range of skills and experiences. Further research will ensure that the elderly have access to driving a passenger vehicle and that they use the safety features. The effect of the variables associated with the individual and the vehicle technology and interaction with the use of driving strategies should also be investigated [70].

The results of this study showed that among MCI individuals more non-professional drivers were not the main family drivers in relation to the professionals (p=0.038). In another study it is mentioned that the caregivers' worry about the patient driving is a strong predictor for the decision of driving discontinuation, in combination with the score in the Clock-drawing Test, which represents 62% of the variance in the decision of driving discontinuation (p=<0.01) [41]. Additionally, in another study it is mentioned that re-assessments of the driving ability based on age are limited in medical tests, which could produce false estimates and unduly reduce the quality of life and safety of elderly drivers [58]. However, in a large study in Ontario, Canada, the results showed that medical recommendations for driving discontinuation could help in accident prevention. Overall, 100,075 patients received a medical warning from a total of 6,098 doctors. There was a decrease of 45% in the annual accident rate per 1,000 patients after medical warning (4.76 vs 2.73, p=<0.001). These data also show that doctors' motives to offer such recommendations increase. Doctors' warnings towards patients who are potentially unsuitable for driving could contribute to the decrease of road accidents, but could deteriorate the mood disorders of patients as well as disturb the relationship between doctors and patients [71]. These practices could lead to the loss of freedom of patients who could be unsuitable for driving [72]. This risk could be reduced with the personalized approach of Occupational Therapy, which would focus on the appropriateness of driving, providing the elderly drivers with the chance to see for themselves how capable they are to deal with their functional deficiencies in more realistic driving settings [58].

Clinicians should make an immediate decision whether a patient is in position to continue driving, while they should recommend further evaluation. All decisions and actions should be documented clearly in the patient information sheet. As in all progressive diseases, re-assessment should be conducted in regular intervals: for individuals with AD re-assessment is recommended every 6 months [73], or sooner, in the case that the caregiver or the family notices a significant decrease in the patient's clinical status or driving skills. Furthermore, it is important that clinicians consult their patients and their families for the predicted decrease in driving ability. In Europe and the USA a research is under way so as to develop guidelines for the assessment of elderly drivers who present syncope [74], stroke [75], dementia [76] and Parkinson's disease [77].

Concluding, it is widely accepted that individuals with AD and MCI have an overall reduced driving ability, they avoid driving under difficult conditions and discontinue it more than the healthy elderly [78]. While in the literature there are several studies among individuals with cognitive impairment, there are no references for those with a professional license. In this study, we tried to describe the driving habits and behaviors of individuals with AD and MCI with a professional driving license, given that driving constitutes an automated process regarding vehicle operation which is more connected with procedural memory. Most MCI and AD patients, who are non-professional drivers, avoid driving in unknown areas in comparison with the professional ones, seems to be a

good strategy/behavior. The results of this study showed that in total the individuals with cognitive disorders and with former professional experience behave better while driving in comparison with those who lack such experience. Further studies with the use of a driving simulator could support these results.

All authors declare that they have no conflicts of interest.

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The neurobiology of dementia: spatial and temporal dynamics of Alzheimer's disease major biomarkers

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Abstract

Dementia, with most prevailing cause Alzheimer's disease (AD), is a condition characterized by memory loss and decline of other cognitive functions, of particular severity to affect one's routine. AD illustrates as an array of symptoms permeating thinking, planning and implementation. It has been commonly described as senility, due to the prevalence of the condition among the elderly, and attributed to the general diminution of body functions. In the past decades, researchers highlighted a single molecular mechanism in the development of AD and confirmed the role of amyloid β-protein (Aβ) in neurodegeneration. However, dementia, as well as AD, is still considered to be prompted by multiple factors and botched processes, including Aβ precursor severing, Aβ deposition and clearance, τ metabolism, protein trafficking, lipid recycling, neuroinflammation and redox signaling. Surprisingly, these processes are affected by aging; metabolism and stress leave their hallmarks in the adult brain during the asymptomatic period, and momentum is imposed by the genetic background. The impairment of cholinergic signaling has been also implicated in AD manifestation. However, recently serotonin (5-HT) signaling, and especially 5-HT_6 receptor functionality, has been emerging as a possible culprit for cognitive decline. These findings accentuate the contribution of mood and emotions to memory consolidation and retrieval and they further emphasize on a multimodal approach in preventing and treating dementia, beyond the classical therapeutic schemes.

Keywords: Alzheimer's dementia - Deposits - Soluble Aβ - Clearance -Tau protein - Risk genes - Sleep

Introduction

At the beginning of the past century, the identification of a peculiar case-disease accentuated memory malfunction during psychological and behavioral evaluation [1]. Sporadic episodes of disorientation and delusion concurred with irritability and hostility, as well as speech impairment and reduced ability for recollection. During the following years mental function was deteriorated and memory disturbances have progressed afar towards lethargy. Upon Auguste D.'s demise, Alois

Alzheimer was able to provide us with the first pathological-anatomical hallmarks of the illness: brain atrophy, neurofibrils - occasionally arranged in bundles replacing normal cell and tissue coherence-, dispersed and numerous deposits, and reduced infiltration, counterbalanced by scattered neo-vascularization. Even today, pre-mortem diagnosis relies primarily on cognitive evaluation. It is assisted by brain imaging, which evolved considerably along with molecular findings, predominantly the purification of plaque content and the characterization of Amyloid beta (Aβ) [2, 3]. However, the final and accurate diagnosis relies on postmortem examination of the patient's brain, using traditional procedures and differential immunostaining [4]. The most striking finding is that abnormal intra- and extracellular τ protein (tau) formations are detected at early age and in asymptomatic patients. Until the evasion of iso-cortical areas (Stages V-VI), seeding of the hippocampal and parahippocampal areas is crucial for the establishment of impairment. The current paper discusses recent findings on the synthesis, deposition and clearance of AD molecular signatures, in view of their potential application in the diagnosis and amelioration cognitive decline.

Localization and processing of Amyloid β

The pervasive presence of extracellular deposits in AD patients' brain, in areas processing memory and cognition, suggested a central role of the formations in disease development [5]. Senile plaques occurrence, size, distribution and frequency increases with age and the severity of the symptoms. As the disease progresses, the plaques appear denser, with a characteristic dark core, likely positive for Periodic acid-Schiff (PAS) and Congo Red, and are occasionally circumscribed by silver absorbing fibrous structures, the dystrophic neurites. Plaque core components are difficult to dissolve and extract, therefore impeding their molecular identification. As the less dense neurofibrillary tangles and vascular (amyloid) deposits coexist with parenchymal plaques and share the same gross temporal distribution and tinctorial properties, it was assumed easier to isolate a molecular culprit from the meningeal walls of patients' brain, while a theory about brain infiltration with serum components has been developed. Finally, two independent groups succeeded to solubilize β-sheet fibrils from both plaques and cerebrovascular areas [6, 7] and characterize the composition and sequence of a novel amyloid "peptide".

Isolated Aβ peptides are actually a mixture of differentially cleaved forms, mainly Aβ40 and Aβ42, the latter prone to aggregation that switch from soluble α-helices to β-sheet fibrils and participate in the exponential integration of monomers into oligomeric assemblies and higher order complexes. Typical and modified amyloid fragments derive through proteolytic cleavage from the integral membrane Amyloid Precursor Protein (APP) [8]. As strongly argued by Glenner and collaborators during the initial attempts of amyloid purification, APP gene was found to localize on 21q21.3 [9]. A possible mis-dosage, and the consecutive ectopic localization and seeding/mis-folding provided some mechanistic insights for dementia, while premature aging and mental decline in Trisomy 21 are still challenging the scientific community [10]. Indeed, point APP mutations (e.g. *Arctic*, *Dutch, Iowa* and *Swedish*) and micro-deletions (e.g. *Osaka*) are associated with increased fibril formations, due to enhanced Aβ production or Aβ resistance to proteolysis [11]. Other forms of early onset familial AD accentuate the role of proteolytic processing. Mutations in Volga kindreds on 1q42.13 (PSEN2) [12] and most importantly on 14q24.2 (PSEN1) [13], identified presenilins as components of the γ-secretase complexes and accountable not only for Aβ42 severing, but also for a waxing Aβ42/Aβ40

ratio. γ-secretase is essential *per se* for the release of Aβ fragments, and the initiation of amyloidogenic processes, though a number of other proteases may be adversely involved, including α- and β-secretases [14]. The contribution of differential processing of APP and of the resulting [15] products in brain physiology has not been fairly investigated. Overall, it cannot be concluded at what form and which order APP fragments and complexes may confer a constitutive, protective or deleterious action, as well as if plaques may incorporate amyloid excess, when Aβ42/Aβ40 ratio is imbalanced, or further propagate parenchyma collapse.

Intact APP is normally synthesized at the endoplasmic reticulum, and secreted as a transmembrane component that spans a limited time at the plasma membrane, exposed shortly to the α-secretase complexes, and then recycled through the endosomal pathway [16]. At a given time point, the majority of APP is localized within the Golgi network. In neuronal cells, APP is transported along axons via the fast orthograde transport pathway that supplies proteins and lipids to the distal synapses and mitochondria, and is has been speculated that lipid enriched areas play an essential role in Aβ processing, accumulation and recycling. Modification of cholesterol and isoprenoid synthesis has been shown to affect the secretion or the intracellular pool of amyloidogenic peptides through independent mechanisms [17]. Pharmacological interventions targeting serum cholesterol levels alter plasma membrane fluidity and subsequently vesicular retrograde trafficking and tubular endosomal network, thus translating the mixed effects of statins on amyloid profile [18]. As only a small fraction of APP is regularly localized within the lipid rafts, the disruption of membrane symmetry may fuel redundant pathways and promote the interaction of APP with proteases or adaptor proteins in a non-canonical manner.

APP is essential for brain physiology. APP knockout, although not lethal, results in altered brain morphology in terms of neuronal connectivity [19], causing reduced grip strength and locomotor activity, and impaired learning and memory that further deteriorate with age [20]. At low doses, APP exhibits neutrotrophic actions, promoting synaptic plasticity and enhancing acetylcholine secretion [21], and further facilitates axonal pruning upon sensory deprivation [22]. The attempt to diminish Aβ production, via β-secretase deletion, was initially considered insignificant to brain integrity [23], but soon revealed responsible for epileptic seizures due to BACE participation in parallel in voltage-gated sodium channel β2 protein processing [24]. *In vitro* experiments showed that Aβ alters potassium channels' activity and immunodepletion induces neuronal cell death [25]. These findings suggest that β secretase has multiple functions and Aβ may moderate neuronal excitability, thus mediate cell rescue. Such properties may explain Aβ upregulation in the injured axons of head injury survivors [26], as well as the induction of APP and the upregulation of Aβ42 over Aβ40 during hypoxia/ischemia-reperfusion [27, 28], with HIF-1α serving as an upstream or downstream effector [29]. It is to note that APP hormetic responses define the transition from health to disease, and one should always evaluate the experimental protocols for their physiological or pathological significance [30]. Finally, the identification of the array of Aβ conformations, exposed another important aspect of amyloid biochemistry, namely its antimicrobial properties: oligomeric Aβ species and protofibrils developed in response to fungal and microbial pathogens [31]. The amyloid aggregates snare invading microorganisms to preserve CNS sterility, and it is speculated that extended and repetitive burden transforms brain anatomy and physiology underlying the progression towards the disease.

Localization and processing of τ protein

Swollen axons and dendrites correspond to the afflicted functional anatomical compartment of the human AD brain. Unlike plaques, the dystrophic neurites are indicative of synaptic loss, dendrite injury, disintegration of neuronal circuitry and inflammatory foci. Over time, intracellular fibrillary aggregates, the neurofibrillary tangles, are building up and fill soma. Upon the completion of neurodegeneration and neuronal death, they are detected as extracellular ghost tangles, while distal axonal and dendritic segments appear as neuropil threads [32]. Such neurites may also be associated with neuritic plaques, surrounding Aβ core structures.

The strenuous efforts of Braak et al showed that plaque formation is a relatively late hallmark of dementia neuropathology [4]. Neurofibrillary tangles do correlate with amyloid plaques, however the anatomical progression of Aβ aberrations towards the neocortex succeeds the establishment of dystrophy in subcortical areas. Intracellular abnormalities (prefibrillary species) can be detected at a very early age, and pre-tangle formation is evident at sub-cortical areas during the asymptomatic period. Silver stained neurofibrillary tangles first appear in the brainstem (locus coerulus) and evade (trans) endorhinal region and neocortex later in life. The stereotypical spatiotemporal progression of neuronal dystrophy is currently used for the post mortem staging (Braak I-VI) of dementia cases, in combination with Aβ immunostaining.

The common feature of dystrophic neurites is the hyperphosphorylation of τ (tau) protein. Normally, natively unfolded τ filaments are hypophosphorylated and individually associate with α and β tubulin subunits in high sub-stoichiometry on microtubular surface [33]. τ phosphorylation results in the gradual dissociation of the complex and hyperphosphorylation leads to microtubule collapse. Besides phosphorylation, τ may undergo acetylation, ubiquitination, truncation, methylation and O-GlcNAcylation [34]. The configuration that τ protein will adopt depends on the type and the extent of post-translational modifications. The initial slight phosphorylation results in a double helical conformation and dispersed, “soluble” abnormal intracellular intermediates. With the exception of O-GlcNAcylation [35], the excessive phosphorylation and the rest of modifications contribute to packed filaments. The transition from abnormal entities to pretangles and neurofibrillary tangles in the course of life and disease, as reflected in Braak staging, is mutually facilitated by the APP background [36]. Yet, as in the case of Aβ, it is unclear whether neurofibrillary tangles and neuropil threads enclose the potentially toxic τ intermediates, compensate cellular inadequacy to cope with dysfunctional proteins or participate in the disruption of axonal transport and synaptic communication [37].

The role of τ in AD has been debated, since the protein has been first isolated in an attempt to characterize microtubule binding factors, and later familial cases have been attributed to Aβ associated mechanisms, despite the immunoreactivity of plaques and tangles for hyperphosphorylated τ [38]. Considering τ solubility and intrinsic disorderly properties, it was argued that microtubules could in fact act as chaperones for τ monomers, rather than the opposite. The identification of MAPT mutations in a number of aggregation diseases, such as Tauopathies and Frontotemporal Dementia endorsed τ protein as an independent agent of neurodegeneration. Out of the 101 characterized mutations on 17q21.31 locus, only 15 have been shown involved in AD pathology [39]. Variants of the MAPT may affect the onset of the disease and the volume of hippocampus and entorhinal cortex. Although the role of particular SNPs in the development of dementia is inconclusive, a cluster of genes, known as haplotype 1 (H1), has been continuously

implicated over the years [40]. Recently, a GWAS of 89,904 individuals showed that the A allele of rs393152, within the extended MAPT locus, confers increased AD risk, especially in APOE ε4 non-carriers [15].

Tau is essential during normal development and adulthood and a structural component of neuronal microtubular complexes. An extracellular form of the molecule is detected in low quantities in tauopathies [41] and AD [42], possibly as a result of misdosage. Tau null mice, though viable, present motor deficits, impaired contextual learning and abnormal sleep-wake cycle [43]. Alternative gene splicing is age- and tissue-dependent [44], while protein isoforms' localization reflects specificity of function at the subcellular level, either nuclear, axonal or terminal [45]. The presence of exon 10 domain, which increases tau affinity for microtubules, coincides with the transition of "fluid" fetal cytoskeleton to the rigorous one in the adult [46]. Similarly, differential splicing underlies the decreased vulnerability of peripheral neurons and Purkinje cells [47, 48], the latter presenting extreme sprouting and short axons, thus rarely fibrillization. Axonal τ controls neurite outgrowth, maintains neuronal polarity and orchestrates intracellular transport along axons [49]. Dendritic τ, located in pre- and post-synaptic terminals, has been shown to affect long term plasticity, especially LTD [50]. The differential post-translational modification, primarily phosphorylation, of tau isoforms, dictates its assembly, subcellular localization and functionality and a delicate balance between unprimed and primed phosphorylation at Thr^{231} by Glycogen synthase kinase-3 preserves microtubule stability under physiological conditions [45, 51].

The Genetics of sporadic AD

The onset of dementia has been a crucial parameter in the diagnosis of the disease and most importantly for its impact on life quality, and possibly on family counseling and screening. However, familial (early) AD accounts for a minor fraction of the cases, and the major identified players alone provide a bare genetic background and a simplistic mechanism of action for the rest of the sufferers. Considering the expanded interactome of Aβ and τ, it would be wise to search for other loci. So far, ApoE-ε4 allele is the only established risk factor for AD, and it is concluded that heterozygosity may precipitate both the onset and the severity of the disease [52]. In addition, the rarer ApoE-ε2 allele, in among the few polymorphisms endowed with a protective action. Because of the complexity of dementia, recent efforts are focusing on genome wide studies and multipoint linkage analysis, rather than single polymorphisms, to determine genes' relevance in disease inheritance, and pooled approaches allow to correct the relative small effect size [53]. In the initial GWAS, ten genes were found to correlate with late onset AD (ABCA7, BIN1, CD33, CLU/ApoJ, PTKB, CR1, CD2AP, EPHA1, MS4A6A-MS4A4E and PICALM3), and including ApoE were estimated to account for half of the total genetic variance [54]. Although it could not be concluded that PPP1R3B polymorphisms are definitely correlated with dementia cases, its role in cholesterol metabolism, along with APOE, CLU and ABCA7, pointed to the need of a more functional analytic approach. IGAP (International Genomics of Alzheimer's Project) researchers joined forces to study moderate contributor genes, based on a pathway analysis, and identified, in addition to nine of the above genes, 11 "new" that participate in inflammatory response, endocytosis, and lipid metabolism [55]. Data pooling reinforced the importance of APP (SORL1 and CASS4) and tau (CASS4 and FERMT2) processing, immune response and inflammation (HLA-DRB5 and DRB1 loci, INPP5D, MEF2C and TREM2), cell

migration (PTK2B) and lipid transport and endocytosis (SORL1) in AD. It also implicated new pathways, such as hippocampal synaptic function and LTP (MEF2C and PTK2B), cytoskeletal function, axonal transport, gene regulation and protein modification (CELF1, NME8 and CASS4), and microglial and myeloid cell function (INPP5D). Overall, data underline the polygenic character of the disease, and scientists are currently exploring a common genetic ground for neuro-susceptibility among prevailing neurological disorders [8] that would also facilitate early diagnosis [56]. A step further, functional expression studies are exploring the effect of candidates risk genes polymorphisms on τ toxicity and fibrillar pathogenesis [57], as well as on gray matter density, brain metabolism and cognitive impairment progression [58].

Neuroimaging and Biomarkers in Cerebrospinal Fluid (CSF) and plasma

Pre-mortem diagnosis of AD and dementia relies on the criteria provided primarily by NINCDS-ADRDA, and also DSM-IV and ICD-10 [59]. A thorough physical examination of the patient eliminates other causes, and in combination with a cognitive evaluation, advises of “probable AD”, with relatively fair positive, but lower negative predictive value, as compared to postmortem examination. The evaluation of biological parameters may facilitate and establish the diagnosis even prior to the symptomatic period, assist the classification of disease progression, and define the relative risk and need for periodic screening in mutation-carrying families’ descents. Different imaging techniques, such as magnetic resonance imaging (MRI), fluorodeoxyglucose positron emission tomography (FDG-PET), or single-photon emission computed tomography (SPECT), allow visualization and semi-quantitative analysis of brain atrophy, hypometabolism and hypoperfusion. Amyloid and τ imaging and measurement of Aβ and τ in CSF are useful in differential diagnosis, confirming AD pathogenesis and delineating pro-dromal stages. The selection of the proper biomarkers and techniques is further essential for the negative diagnosis, to assure greater predictive value. The IWG and the NIA/AA work groups support the diagnosis of AD prior to the onset of symptoms and pervasive cognitive decline, however, the proposed terminology is confusing for the clinical practitioner, as well as the stratified and not uniform implication of biomarkers discriminating amyloid abnormalities from neurodegeneration. Scientific evidence of biomarkers’ strength and specificity along the course of disease is necessary to improve the applied criteria.

In fact, at least the two major components of familial AD, Aβ and τ can be detected in soluble forms in the CSF. Surprisingly, as disease progresses Aβ diminishes and total [and phosphorylated] τ increases. The two components show a “complementary” pattern- they wane and wax by the same factor, and the change can be early detected during the latent period [60]. On the contrary, cortical amyloid deposition, as detected by PET PiB, correlates positively with τ and phospho-τ (p-τ) levels [61]. A follow up of patients with moderate cognitive impairment showed that the shift in τ and P-τ levels is enhanced by the rate of cognitive symptoms deterioration [62]. Despite the detection of hypephosphorylated tangles, the diffusion of τ outside the cells, and the net increase in P-τ levels in AD, relative P-τ levels are lower than the one in controls or individuals at the early phase. Aβ42/P-τ ratio though is sufficient to provide both positive and negative AD prognosis, with approximately 90% accuracy.

Aβ40 and Aβ42 can be also detected in plasma. Their concentrations reflect relative brain load, but they provide a steady profile, quite independent of age, gender, and stage [63]. When compared

to CSF τ and P-τ, and functional imaging data, no statistically significant relationship was found [61]. Participants' age and grouping may affect the consistency of the findings. By applying plasma Aβ median as cut-off, Llado-Saz et al showed in an elderly population that peripheral amyloid species are associated with cognitive performance: higher Aβ40 correlated with prefrontal cortex thinning and poor objective memory, whereas higher Aβ42 correlated with atrophy of the anterior temporal lobe, poor everyday memory and increased homocysteine levels [64]. Furthermore, albumin bound Aβ is also decreasing with age, and major depressive disorder patients exhibit higher soluble Aβ40/Aβ42 ratio [65]. On the other hand, plasma τ protein is difficult to detect and quantify. Recently, using an ultra sensitive assay, Zetterberg et al were able to detect concentrations <1ng/l. Total τ was higher in AD patients, but no correlation with CSF τ or within groups difference was found [66], while the relationship between peripheral Aβ and τ levels was not investigated.

The temporal dynamics of CSF Amyloids and the impression of sleep quality

Among the most important findings during the study of CSF solutes was the intra-individual variation of Aβ40 and Aβ42 levels. The method of sampling, the use of separate lumbar punctures or of lumbar catheter and filter, may affect the result, but time and draw frequency had the most profound effect [67]. A gradual upward drift was generally noted for both analytes and the observed increases did not return to baseline at 24 hours or even after extended sampling for as long as 36 hours. Normalization of baseline was only observed at the endpoint of a two week study. In all cases, a diurnal pattern emerged within the slope, presenting a simultaneous peak for both Aβ40 and Aβ42. Peak time and amplitude varied between interventions, possibly due to the differences in sleep-wake cycles and age respectively. Indeed, subjects positive for amyloid plaques showed lower average Aβ42 levels, and a threefold decrease in Aβ42 variability, as compared to age-matched controls and young subjects [68]. Hourly Aβ40 variability, but not mean Aβ40 values and overall variability, did differ among groups. Aβ40 circadian patterns followed a cosinor fit in all participants, as well as Aβ42 variations in the young, and exhibited peak amplitude around 10 pm. The effect of age and amyloid deposition was greater on Aβ42, as it reduced amplitude down to 80% and concealed the diurnal variation [69]. Sleep duration has a positive effect on CSF Aβ42 levels. In addition, sleep-wake cycle is important for Aβ42 clearance and turnover, and sleep deprivation abolishes Aβ42 nocturnal rise and circadian pattern, without affecting Aβ40, τ, P-τ and total protein levels [70]. Impairment of circadian rhythm during the early AD stages is not confined to brain parenchyma. Skin fibroblasts show *ex vivo* a 6h phase lapse and reduced amplitude in the expression of the core clock gene BMAL1, and a receding Per2 response [71]. The advancement of transcriptional activity in cells from non-AD donors may be justified by aberrant methylation in AD, as cytidine analogs and S-adenosyl methionine normalize promoter response in a dose-dependent manner.

SNP-focusing and GWAS studies had concluded that polygenic input defines the onset, type and progress of dementia, and overall the identified loci may explain 80% of the genetic variance. On the other hand, genetic variability may resolve half of the phenotypic variability [72]. Therefore, the impact of extrinsic and intrinsic environmental factors, on a given background, is considered essential for the development of AD. Age is definitely a primary risk factor for neurodegenerative phenomena and the manifestation of related disorders. Besides the metabolic changes in the elderly, circadian rhythm is afflicted, including sleep duration, ease and coherence [73]. Such changes are

detected upon AD manifestation, but they may also occur prior to severe cognitive decline. Individuals with abnormal CSF Aβ42 levels (≤500 pg/mL) are more likely to sleep less in total [74], whereas sleep disturbances may predict symptomatic AD or related death within a 5-year window [75]. The contribution of sleep-wake cycle in amyloid metabolism has been recently shown in a mice experimental model, where γ-waves application facilitated amyloid deposits clearance by the glymphatic sytem [76]. In humans, it is plausible that AD amelioration and reduced mortality, as documented by the wide use of cholinesterase inhibitors, may be due to the essential role of cholinergic system in time registration and temporal memory organization [77].

Thalamocortical projections' cholinergic tone is indispensable for the transition into the REM phase, allowing cortical neurons to act independently. This type of desynchronization is normally illustrated as divergent alertness to environmental cues during sleep [78]. Serotonergic system output during sleep-wake cycle is more complicated and state-dependent [79]. Serotonergic tone is gradually diminishing through sleep states, and tone disruption is followed by sleep disruption and initiation of wake, as seen in depression. In AD, 5-HT neuronal loss, down to 40%, was first described in raphe nuclei-responsible for sleep regulation, with loss being more prominent with patient's age [80]. The anatomical changes are reflected in decreased serotonin production, from brainstem to the cortical areas, as well as in amygdala, caudate nucleus, putamen, and hippocampus, and correlate with intracellular tangles, reduced cognitive performance, as well as with behavioral symptoms, depression, aggression and psychosis. Along with monoamine hypothesis [81], AD pathophysiology [82, 83] suggests that modulation of the serotonergic system could improve patients' symptoms. In addition to the benefit on mood and sleep, specific targeting of serotonin receptors 5-HT_{1A} and 5-HT_6 could facilitate memory acquisition and consolidation, and LTP [84] and possibly microglial function [85]. Contrary to the concept of reduced serotonergic and cholinergic in AD brain, 5-HT_6 antagonists, including idalopirdine and RVT-101 that undergo phase III clinical trials, aim to further reduce serotonin signaling and reverse cognitive deficits by "attenuating cholinergic or glutamatergic signaling" [86]. Interestingly, co-administration of the 5-HT_6 receptor antagonist SB-271046 with AChEI galanthamine in learning impaired rats resulted in additive/synergistic effects [87]. It is to note that 5-HT_6 expression is detected in the molecular layer of aging, but not younger, prefrontal cortex and is compromised in AD neocortical pyramidal neurons and inter-neurons, as compared to age-matched controls [88]. It is possible that the novel promising candidate compounds improve cognitive function through a direct and indirect mechanism, by having serotonin displaced and readily available to 5-HT_6 deprived areas.

Conclusions

The vast neurodegenerative phenomena in the aging brain and the conditional emergence of symptoms in AD point to the hierarchical deterioration of neuro-modulatory axons. Despite our limited understanding of the dynamics of Aβ and τ, it is concluded that the initiation and progression of symptoms are context dependent, and even events during early life may have long lasting structural and functional consequences [89]. Current pharmacological interventions do not address the whole array of dementia facets [18], therefore complementary and intuitive strategies may be useful in preventing or delaying cognitive impairment [90]. As the quality of life has immediate, distant, but to a considerable degree, recuperative and reversible effects on brain metabolism [91], a

multimodal approach would assert a clinically favorable outcome.

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The author declares that has no conflicts of interest

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Media enhanced educational and training interventions for people at risk of Alzheimer's disease

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Abstract

Changes in cognition observed in Mild Cognitive Impairment (MCI) syndrome can be noticed by individuals and their families and in most cases this is the reason for asking for medical advice. Later on, computerized cognitive skills training and screening services are offered to sense those conditions and to numerically express the changes in cognition over time. This paper describes a web-platform designed to offer skills-training interventions to people at risk of developing Alzheimer's disease (AD). The content development was based mainly on verbal fluency and other combinatorial mental abilities judgment. One hundred fifteen (115) people, aged 55 to 78 years old (M=65.57, SD=5.89) were recruited in a proof-of-concept study (92 MCI/ 22 healthy controls). The results indicated that the systematic use of language in computerized interventions could provide an additional diagnostic and skills-training value for the management of the MCI patients.

Keywords: Mild Cognitive Impairment - Language - Computerized Screening Batteries - Education - Skills training - Cognition

Introduction

Mild Cognitive Impairment (MCI) is associated with memory loss complains and/or cognitive decline, but this does not affect daily functioning and social inclusion [1]. Early diagnosis and intervention is important to prevent progress to Alzheimer's disease (AD) for people with MCI.

From the limited pharmacological interventions for dementia currently available we can mention Donepezil, Rivastigmine, Galantamine and Memantine, which have been approved [2], but good clinical practice requires the clinician to try also non-pharmacological interventions before considering pharmacological approaches or in combination [3]. Combination solutions which use both drugs and non-pharmacological interventions to slow down the progression of cognitive decline and to strengthen the quality of life are very popular and effective.

Those non-pharmacological interventions refer to both environmental and behavioral modifications and include but are not limited to validation, reminiscence, behavioral and interpersonal therapies, multisensory approaches, brief psychotherapies, reality orientation and also

activity therapies. The roots of this study lie on Cognitive-Behavioral Therapies (CBT) which implements series of problem-focused multisensory tasks targeted to reduce symptoms by learning new information-processing skills [4, 5].

Language trajectories during aging and in MCI

Language trajectories by aging have been researched since early investigations in cognitive aging [6]. Among negative effects of aging is the use of oversimplified speech by older adults in order to preserve a familiar level of social interaction, but basic language functions remain quite stable during aging [7]. It has to be noted that -in general- those findings refer more to spoken language than written and more to language production than comprehension. Overall, one of the most important conclusions of the related research is that working memory limitations can cause language deficits [6] and that there is no decrement in semantic processing of language in normal aging [8]. On the other hand, specific language abilities like reading comprehension, verbal fluency and narrative ability are affected in MCI, although they remain intact in normal aging [9].

Based on the above, the use of complex language may require advanced language processing and thus it may differentiate people having MCI from people free of Dementia symptoms (normal controls). This is the main hypothesis of this study: that people with MCI is expected to have worst performance on language tasks because of a worst language slowing process than normal aging. Those tasks have to be targeted on specific language functions which are more affected by MCI, like complex syntactic processing for example [6]. This worst performance expected by people having MCI does not refer only to the score (success rate), but it can be also extended to the time needed to complete tasks (duration) based on the theory that people with MCI have a steep decline in processing speed.

Computer-based Assessment and Skills Training

The computerized cognitive assessment has been proposed to fulfill the need for fast and efficient testing and to overcome limitations like the presence of trained personnel in place. Historically, the computer-based testing and mental health condition monitoring was initiated by the adaptation of the existing testing and interventions materials in computerized environments under the benefits of accurate assessment, low cost and time-saving administration, availability and applicability to various clinical and non-clinical settings [10].

In this line, various proposals for computerized tools, including validity tests, have been presented like the CANS-MCI [11], CANTAB [12], MicroCog [13], CogState [14] and Mindstreams [15] and other 23 at least. More complicated environments, like web-platforms, have been proposed in the literature to offer a centralized environment for managing screening as well as cognitive training exercises. For instance CogWeb [16, 17] includes 60+ cognitive training exercises delivered by a web-based platform for remote interventions (living environments). In another example, the computerized self-test (CST) [18] assesses orientation, visuospatial abilities, verbal fluency, memory, attention, and executive processing using screens for tasks like the clock-number and animal naming. The principles of the accessibility design or the design-for-all have been taken into account for not excluding users with visual, acoustic or motor disabilities.

Existing computerized approaches may distinguish the screening and user monitoring from therapeutic interventions. Thus, in most cases, users of computerized interventions have to learn an

additional software tool before actually participate in computerized therapies. Another limitation of most existing interventions is that they rely mainly on simple textual or graphical stimuli. The next section explains how the user screening and the skills-training interventions have been combined in a single environment to offer novel interactive and media-enriched linguistic tasks.

Platform and Content Design

Within the current study interactive multimedia activities were targeted to main language abilities as verbal fluency and reading comprehension in different levels (word and sentence level). Those were implemented by tasks which require cognitive resources -apart from working memory- executive function, syntactic/grammatical assessment, semantic ability, visuospatial and attentional control. To be noted that tasks to test narrative ability were not inserted in this implementation because it would be difficult to comply with the followed model of computerized cognitive assessment.

Those tasks were designed to engage and stimulate the elderly people and people with MCI for participation in user monitoring and cognitive skills training in a regular basis. This was achieved by: 1. content circulation and randomization, 2. the use of multimedia in stimuli (drawings, photos & videos) and 3. the use of interactive visual controls. More information on the type of playful tasks and their relation to specific methods of assessment can be found on Table 1.

***Table 1**. Short Description of the linguistic tasks*

Name	Description	No. of subtasks
Word Ordering	Sentence construction based on scrambled words. Users re-order words to make meaningful sentences.	Four (4) sets of words in randomized order to make 4 sentences
Select Improper Sentence	Written text comprehension in which test patients try to select and erase an inappropriate sentence.	Three (3) paragraphs to choose 1 sentence from each
Anagram	Given a set of letters, users try to construct words, like the scramble game.	Four (4) photos and 4 sets of letter to make 4 words
Fill The Gap	Given a set of sentences with a missing word (blank) and a set of words, users try to make the matching: Fill the gaps with the given words without replacement.	A set of 12 words to select one for each of the 5 sentences

Name	Description	No. of subtasks
Reading Comprehension	A typical reading comprehension task to test for the ability to read text, process it and understand its meaning	One (1) paragraph and 7 questions with 3 multiple choices each
Dialog Comprehension	Matchmaking task in which test givers try to find the social context in which a dialogue between two people is taking place.	Two (2) pairs of questions-responses (stimuli) to choose 1 out of 4 images
Dialog Construction	Filling sentences in a dialogue context. Test patients try to fill missing parts of a dialogue based on interlocutor's response.	Five (5) responses given as stimuli for which the questions are missing (having 3 options each)
Sayings/Non-literal expressions	Metaphoric sentences comprehension. Users try to give an interpretation of the meaning of the sentence (saying)	Four (4) non literal expressions with 2 multiple choice options each
Werb Forms	Filling in the proper grammatical type. Given a verb, test patients try to give the right grammatical type to fill the blank in a sentence.	Six (6) sentences having one blank each to be filled by free text

The language stimuli (content of the language tasks) were provided in Greek language. Also, the interfaces of the platform were designed for people who experience disabilities to ensure direct access to the platform and its content (i.e. unassisted personal use) according to common accessibility standards (WCAG 2.0[1] guidelines) and the design-for-all principles (ETSI Guide Human Factors[2]).

Pilot Study

The proposed interventions were empirically tested by two groups of people: a. people with MCI and b. healthy controls (HC). Those people were visitors of the Alzheimer's Day Care Unit 'Saint John'

[1] Web Content Accessibility Guidelines, v.2, https://www.w3.org/TR/WCAG20/

[2] Human Factors (HF), Guidelines for ICT products and services: "Design for All", www.etsi.org/deliver/etsi_eg%5C202100_202199%5C202116%5C01.02.02_60%5Ceg_202116v010202p.pdf

located in Thessaloniki, Greece for a two weeks study.

Preparation

All participants went through a standard neuropsychological assessment based on well-established screening batteries like the Mini Mental State Examination (MMSE) [19], the Rey Auditory Verbal Learning Test (RAVLT) [20], the Test of Everyday Attention (TEA) [21], the Making Test Part B (TMT-B) [22], the FAS (the equivalent 'ΧΣΑ' in Greek language) [23], the Functional Rating Scale for Symptoms of Dementia (FRSSD) [24] and the Clinical Dementia Rating (CDR) [25].

One hundred and fifteen (N = 115) elderly people, aged 55 to 78 years old (M = 65.57, SD = 5.89) participated in the study. After the neuropsychological assessment and a face-to-face interview with the clinicians of the hosted institution, 92 were diagnosed with MCI and the rest 22 were the group of HC. All participants were native Greek language speakers and they were attending computer classes at the time of the platform testing and thus they were confident computer users.

The two groups of participants were matched according to age ($t(98) = -.816$, $p = .417$), gender ($t(103) = .096$, $p = .924$) and level of education ($t(89) = -.701$, $p = .485$) expressed in here as years of received education.

Protocol

Participants were entering a computer lab in groups of 10 people at maximum. Each person had the chance to test the platform for two or more times after a few days' brakes. All workstations were equipped with a personal computer (PC) with touch-screen and typical input peripherals (mouse, keyboards). Before the actual testing of the proposed platform all participants had an introduction, a live demonstration of the online activities and discussion. In addition, the responsible researchers explained the purpose of the study and asked participants to fill up a consent form. All processes were designed and performed according to the ethics of the hosted institution.

Two performance metrics were used in this study: 1. the success rate (correct answers to the total number of questions) and b. the time needed to complete each task in seconds. An objective method was used for performance monitoring based on log file analysis. According to this, all interactions of the users were recorded at the time of the test and saved by the computerized environment in a secured information space for later analysis. This approach gave certain benefits like the personalized user monitoring, accuracy in measures and immediate reporting of results.

Results

After the testing sessions -up to 2 hours- the log file analysis resulted that the proposed language activities require more time to be completed for people with MCI than for HC. Not only statistically significant differences were found in the mean durations of the overall test between the two studies groups (Table 2), but those differences were tested against their ability to discriminate the MCI symptoms. Also, it was observed that computerized language activities require more time to be completed for people with MCI than for HC. Indeed, according to the Mann-Whitney statistic, both the total score ($U = 131$, $p = .004$) and the time needed to complete all tasks ($U = 115$, $p = .001$) were different at a statistically significant level.

Apart from the content of the skills-training tasks, the functional testing results indicated that the

proposed training platform met the requirements of the users and the specifications of a typical computerized skills-training environment. None of the test-takers quit the screening and training sessions and all reported that they understood the interfaces of the linguistic tasks, especially after the live demonstration before the actual testing.

***Table 2**. Means scores in the linguistic tasks*

Metric	Score (Standard Deviation)
HC	
Score (Standard Deviation)	34.466 (SD = 2.748)
Duration (Standard Deviation)	914 (SD = 150)
MCI	
Score (Standard Deviation)	31.222, SD = 4.106
Duration (Standard Deviation)	1343, SD = 480

In overall, the results of the experiment indicated that media and interaction enriched language exercises have a remarkable diagnostic and a skills-training value. The later can be supported by the fact that after only two weeks of using the educational platform, all groups of participants showed a noticeable increment in their learning outcomes. For those who had completed all tasks during the first session and repeated the test a second time (N = 35), it was found that the later scores were higher than those of the first session by around 10%. Moreover, no statistically significant differences were found on the time needed to complete the test among the participants of the two groups (healthy controls and MCI).

Discussion

This study aimed to generate experimental evidence that the patterns of language performance in MCI are significantly different than normal aging and this is of particular interest for screening purposes. Our approach combined Cognitive-Behavioral Therapies (CBT) and multisensory approaches using Information and Communication Technologies (ICT) in a game-like environment which delivered interactive and media-enriched linguistic tasks. Services on offer were targeted at training short-term memory, selective attention and linguistic processing for prevention and screening for MCI conditions. Apart from expected benefits of the computerized interventions like the hands-on results [26] and the ability to compare results between user groups & sessions [27], this approach achieved a high user's acceptance rate, good first skills-training results and all of the above were achieved under a limited learning effect. Standard practices to eliminate learning effect were applied like the randomization of the tasks and the circulation of questions.

The results of this study comply with similar research findings which connect sentence-level processing problems with decreases in executive function and memory in all dementia syndromes [28], as well as executive function with sentence processing [29]. According to other studies with an interest in timed tests [30], it was confirmed that the time needed to complete the propose language tasks can be sensitive to the language declines related to MCI. Overall the use of complex language,

in terms of syntactic reasoning requirements [31], can be an important element when designing screening instruments.

As in most computerized approaches, there are some limitations coming from the fact that there is a lack of widely approved psychometric models and it is quite challenging to make direct links between the previous clinical praxis with the new computerized interfaces [32]. Regarding the training contents of the platform we have to note that previous education may have an effect on the most difficult linguistic tasks. Moreover, ICT-based solutions for skills-training and user's progress monitoring require that people have at least the basic computer skills. Distant online training could supplement and offer valuable feedback in existing clinical practices.

Conclusions and Future Plans

This work proposes a set of cognitive-training interventions using computerized interfaces to train short-term memory, selective attention and linguistic processing. New modalities, the use of speech and the rich media inserted into the cognitive skills training protocol created added values which are increasingly important to monitor the cognitive functions at risk in the early stages of dementia.

In addition, we confirmed that computerized educational/diagnostic interventions have a number of advantages over traditional paper-and-pencil tools such as time and cost-saving and the accurate data recording for decision support. Also they provide the opportunity to compare the performance of patients between different MCI development stages and have positive side effects as cultivating computer-training skills.

Future plans include a test-retest reliability study using the very same linguistic tasks, under the same conditions and in short period of time, compared with the progress of the MCI symptoms in order to be concluded if the proposed screening measurements can be said *repeatable*. In parallel, we will have the chance to further study the effect of the skills-training environment over larger populations of interest.

All authors declare that they have no conflicts of interest.

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From e-homes to living labs: founding and organising the Greek active and healthy ageing living lab (Thess-AHALL) and its networked services

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Abstract

With economic crisis severely impacting multiple facets of everyday life, research/academic activities, as well as, social care services, any emphasis on researching or establishing suitable elderly healthcare services becomes questionable in terms of success and sustainability prospects. On the other hand, the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA) promotes the exploitation of technological innovations for ageing and calls for reference sites, to promote and share best practices. Although key technological advances have been improving the possibilities of seniors' active participation in daily social life, there is still ample space for improvement in all facets. To this respects infrastructures such as e-homes were attempted in the recent past in an effort to configure optimal ways of introducing senior people to modern technologies while satisfying the requirement of ecological validity. However, a more contemporary concept, that of a living lab, has recently emerged. Thus, the aim of this paper is first to illustrate the process of founding the living lab in Thessaloniki, dedicated, to start with, on active and healthy ageing studies (Thess-AHALL). As a second goal, the paper systematically describes how Thess-AHALL complies with guidelines of the European Network of Living Labs, so that it expands it joins the network and expands its services by promoting co-creation in a sustainable, open and innovative way. It is expected that this compliance exercise will be useful as a guide to a wide range of interested parties and may become the reference any similar endeavor.

Keywords: Elderly Healthcare - Ecosystem -Co-creation - Co-piloting - Living lab - Networked services - Elderly -EIP on AHA - Ambient Assisted Living - Independent living - Social innovation - Sustainability - Openness

Introduction

Undoubtedly, the ageing problem forms one of the key societal challenges of contemporary life in the developed part of the globe. Much has been discoursed in scientific meetings and conferences about best approaches in tackling it, while numerous initiatives have been driven by governments as well as non-governmental organisations with an aim to unite forces and achieve best practices for the widest possible application. In a book-chapter published recently, it has been concluded that

although important technological steps have been made towards new interfaces for the elderly, thereby improving the possibilities of seniors' active participation in daily social life, there is still ample space for improvement in all facets [1]. Infrastructures for eHomes, of any purpose, emerged as a viable way for managing elderly healthcare costs as well as facilitating related research [2]. After several years of maturation, current solutions are challenged with technical and sustainability issues. Moreover, slowly but surely though, the jargon term of Ambient Assisted Living (AAL) and its associated platforms and technologies were replaced by the new key term of Active and Healthy Ageing (AHA) in an attempt to denote the dynamic capacity of contemporary care in activating the elderly while providing improved care [3].

Back in 2014, while attempting to configure the optimal way of introducing senior people to modern technologies towards the organization of field trials in their own homes, it was thought that perhaps the creation of an e-home would help, thereby satisfying the requirement of ecological validity. Conceptualising the technological and organizational components of such an endeavor, it was also deemed that perhaps a better approach would have been the creation of a living lab instead.

Living Labs refer to "user-centred, open innovation ecosystems based on a systematic user co-creation approach integrating research and innovation processes in real life communities and settings" [4]. Facilitating the above scenario in practice, the notion of a living lab could place the elderly citizen in the core of innovation and exploit the ability to harness the opportunities offered by new ICT concepts and solutions to the elderly needs but always contextualized by local cultures and personalized attitudes. With this mind, the authoring team founded the Thessaloniki Active and Healthy Ageing Living Lab, namely Thess-AHALL [5], which soon after became an adherent member of the European Network of Livings Labs (ENoLL).

The aim of this paper is to revisit this process and provide the key constituents for its facilitation and expansion. In so doing, emphasis is drawn upon providing the motivation behind it and its hand-shaking with ENoLL, as well as, its organizational structure and potential to systematically orchestrate and conduct high quality applied research in the elderly healthcare domain.

Methodology

After describing its setup, and to explain how Thess-AHALL complies with the principles of co-creation and co-piloting, the current piece of work systematically examines the guidelines of ENoLL, and compares the actions of the former to join the network of the latter. Key questions examined in each of the compliance elements are innovation and sustainability, as well as, the involved interaction cycles and obtained benefits, as shown in Table 1.

Table 1: *Compliance items for Thess-AHALL to principles of co-creation, open innovation and sustainability. Each item is examined along elements of the innovation process and the interaction with as well as benefits for different stakeholders to infer sustainability.*

Compliance item	Elements of the innovation process	Interaction with / Benefits for

Activities and services engagement	all phases; co-creation and co-design of technologies	user groups and stakeholders
Organisational structure	Capacity to replicate / expand	International Associations, Social care stakeholders, SMEs
Openness	Social Innovation, Open Technology Platform, cross-device/application communication framework, Open Innovation	Open Knowledge Foundation-Greece, SMEs, users, Attractive, cost and time effective pilot trials with seniors
Resources	Dynamic infrastructure of ecologically valid and networked environments, Business, finance and expansion capacity	LLM Care ecosystem
Value creation	co-piloting model for conducting pilots with seniors, service innovation life cycle advisory	SMEs, Start-Ups, Research groups and academia, Venture Capitals, Organizations dealing with ageing citizens, caregivers and family members
Users and Reality	participatory design, appreciation of the socio-economic implications of the living-in-place process, rigorous User-Centred, Inclusive Design	Greek Association of Alzheimer Disease and Relative Disorders, Parkinson's Association of Northern Greece, LLM Care ecosystem sites

Background: setup of Thess-AHALL

Thess-AHALL has been operational since the summer of 2014 and is based in the city of Thessaloniki in the Central Macedonia region (Northern Greece). The lab fosters initiatives encouraging regional development and healthcare systems sustainability by the provision of novel technologies and innovation. The lab is actively engaged with end-users and relevant community stakeholders, actively pursuing co-creation and co-design of technological solutions to improve health and social conditions and facilitate independent living. Our paradigm involves open innovation through open data schemes and makes the end-user an actual driving force for innovation instead of just a consumer/spectator. Apart from actions centred in the main environment, the lab actively engages in international activities, in research and innovation actions, networking, technology transfer etc.

The ultimate aim is to facilitate the speeding up of innovation, collaboration, development and testing of more accurate services, which is achieved by the early involvement of users as co-creators. The strengths and capacities to do so, lie within the following:

- The operation in actual community settings and residences following a paradigm of actual in-the-wild collection and processing of data, employing as much as possible ecologically valid schemes [6, 7]. A network of senior homes [8] and nursing homes or day care centres are live paradigms of naturalistic environments, where innovation and user involvement takes place. Our vision involves the community and profits from the community's input to promote and disseminate actions and

innovation that foster real needs of real people in real environments [9, 10].

- Its strategic geographical location and its wide, trans-national network. Thess-AHALL is the only active Well Being and Health Living Lab in Northern Greece and the Balkan region in general. The strong collaboration prospects of the Living Lab and its impact on research centers in Low and Medium Income Countries in the Balkan region (cross-border projects already active; see for example the Smokefreebrain project www.smokefreebrain.eu) as well as with Cyprus, justify its strategic geographical location. Moreover, the Lab co-ordinates activities in scenario based learning and virtual patients in a supra-regional way by controlling and managing work and capacities with post-Soviet countries like Ukraine, Georgia, and Kazakhstan (see for example the ePBLnet project, www.epblnet.eu). Therefore, Thess-AHALL, can subsequently act as a success case for other regional and supra-regional parties, and further disseminate its activities to motivate them to join ENoLL network as well.
- Strong Collaboration with: the AHA ecosystem in Greece through the LLM Care ecosystem [10] (www.llmcare.gr) and wide access to elderly nursing homes, daily care centres, municipalities, Regional Health Authorities of Attica, Central Macedonia, Greece, and numerous elderly care day centres of the Greek Federation of Alzheimer's Associations. Through the LLM Care ecosystem, an established self-funded initiative in technology driven elderly social care [9], numerous such stakeholders are already using the developed services (see http://llmcare.gr/el/map).
- More than 8 years of experience in User driven innovation and evidence-based research in the AHA domain. In the realm of different EU projects, more than 500 elderly people and more than 100 care givers were actually engaged in designing and pilot testing activities, thereby supporting evidence-based research in validating products and services for elderly people and societies. Thess-AHALL is a pilot partner of EU consortia, like the UNCAP and the iPrognosis projects.
- Big, heterogeneous volumes of data (behavioral recordings such as movement, activity levels, emotion and physiological signals, neurophysiological recordings such as EEGs, neuropsychological assessment tests, interventional data: computerized cognitive and exercise games) stemming from the large scale pilots with seniors.
- Big Data infrastructure that is open to European researchers from both academia and industry [11, 12]. Closer interactions between larger number of researchers active in and around a number of infrastructures facilitate cross-disciplinary fertilization and a wider sharing of information, knowledge and technologies across fields and between academia and industry. The open e-infrastructure, when combined with the collection of open Big datasets, offers an unprecedented chance to access at low cost, high quality user-produced data.
- Business plan development for self-sustainability requires the active involvement of: (i) Small Medium Enterprises (SMEs) and industry from the demand side of innovative ideas and (ii) knowledge, society, elderly people and social services from the supply side of innovative ideas and knowledge.

Activities and services engagement

Thess-AHALL's activities encompass all phases of the innovation process. Beginning with the co-creation and co-design of technologies in direct collaboration with user groups and stakeholders, passing to research and prototyping, pilot design and methodology validation to market analysis and

implementation of business plans and commercial exploitation of results.

More specifically, the lab engages in services like:

1. User requirement collection and analysis from direct contact (focus groups, face-to-face interviews) with end users and stakeholders, to produce functional specifications.
2. Design and implement solutions on architectures and technical specifications based on the first step of co-design and co-creation process.
3. Pilot and validate the developed solutions (prototypes, pre-commercial or commercial products) in ecologically valid environments. The solutions are validated on a functional, usability, scalability and (medical) efficiency scale.
4. Cooperate with multidisciplinary consortia to transfer technology, know-how and research results, actively pursuing an improved path from lab-to-market.
5. Market and business analysis and planning for commercial deployment of validated technologies.
6. Training services for the healthcare workforce, especially elderly people care givers, based on electronic platforms and standards, such as virtual patients [13] (see the Discover project and (Sidiropoulos et al, 2015)).

Finally, it is worth mentioning that Thess-AHALL is well connected to other relevant initiatives and Institutions, via EU-funded projects.

Organisational structure

The host organization of Thess-AHALL, i.e. the Laboratory of Medical Physics, School of Medicine, Aristotle University of Thessaloniki, sustains links to a wide network of oganisations such as the International Federation for Medical and Biological Engineering (IFMBE), the European Alliance for Medical and Biological Engineering and Science (EAMBES), the Greek Society of Biomedical Engineering (ELEVIT); a wider network of stakeholders through the LLM Care ecosystem. A lot of organizations have invested in or sponsored this initiative with the most recent example of TIMA (non-profit charitable foundation) based on which Thess-AHALL expanded with a living lab copy and associated technical installations in the Chariseio nursing home of Thessaloniki, Greece, a care provision center with senior residents. This living lab instantiation is essentially a replica of the main Living Lab set-up. Visited constantly (over the year) by elderly people, the living lab fosters the early involvement of elderly people (the customers) in the development as well as commercial product evaluation (www.aha-livinglabs.com). Links to local governmental structures are key to success. Thus, there exist cooperations with the municipalities of Thessaloniki, Pella, Orestiada, Holargos and Papagos, as well as, different Regional Health Authorities (RHAs) and non-governmental organisations like the Greek chapter of Open Knowledge Foundation (OKFN).

Users: People suffering from different types of cognitive impairment: Elderly people: elderly people in good health status and patients suffering from mild cognitive impairment, depression and their caregivers; People with disabilities: Children/youth with special educational needs (ADHD). Health professionals: psychiatrists, psychologists, neuro-psychologists, gerontologists, occupational therapists, social workers, etc. In general, professionals working in care settings and in the community, participating in our research and work lines and using technologies to support their social and healthcare activity.

In order to ensure the smooth running of the AHA Lab, coordinating the various initiatives and

projects, the organisation of the lab is broken down in the following:

-The director (currently at the level of Associate Professor).

-Advisory Board which works as a steering committee comprising multiple experts, providing insight regarding issues of open Data, technical and scientific advice and ethical/legal aspects.

The Group Leaders: People responsible for the laboratory's sub-groups, namely the Assistive Technologies and Silver Science Group, the Medical Education Informatics Group and the Applied and Affective Neuroscience Group

The Lab Managers: Members of the AHA-LL managing the every-day activities of all the participating sites, from purely technical aspects to communication with users and data collection.

Business Development and Dissemination Group: This group is responsible for disseminating the results of our research projects and exploring business opportunities, as well as managing the lab's spin-off company.

R&D Group: A big group of multidisciplinary researchers, students and professionals who are responsible for all ongoing research of our lab.

Figure 4. Thess-AHALL organizational structure

Openness

Thess-AHALL is based on the User-Driven Open Innovation methodology that amplifies impact on the territory towards Social Innovation, co-creation and co-design through active participation of users and citizens with a view to evolve products and technologies in real life contexts. On the one hand, openness increases the potential of high technology to create and/or attract high-tech entrepreneurships, while on the other, employs and uses high technology to contribute to the modernization of the socio-economic system. Thus, the living lab becomes a powerful and open tool

for effectively involving users in all stages of research, development and innovation, thereby contributing to the growth of competitive regions. The benefits for the different ranges of figures related to the open-ecosystem created are:

- Users in their roles as members of the community: they are empowered to influence the development of products and services that serve the real needs and to jointly contribute to the savings and processes through active participation in the life cycle of the product / service.
- SMEs and micro-enterprises: new ideas are developed, validated and integrated; their services and products will be growing rapidly moving from concept to design, lab evaluation, real homes evaluation, local markets to other markets. Efforts for strong collaboration with other Living Labs (members of ENoLL) towards a virtual cross border living lab as a service, will transform the evaluation from local oriented to other countries.
- Large firms: the innovation process becomes more effective, through alliances with other companies, and early interaction with representative groups of end users, which are validated in the active experience with users, thus increasing the probability that the new product/service will have success already at its first appearance on the market.
- Active subjects in research, economy and society: the partnership among businesses, citizens and governments is established to set up a real ecosystem of innovation and flexible service, which integrates social and technological innovation, and increases the productivity of investment in R & D.
- Attractive, cost and time effective pilot trials with seniors: Thess-AHALL has already designed, developed and made publicly available an online tool (CAC Playback Player) for reproducing the collected datasets, of pilots that have already been conducted in the LL, on demand by streaming so that the pilots are reproduced as if they were taking place in real time, (http://www.cac-framework.com/app/#/playbackmanager). Therefore, by eliminating the cost and complexity of conducting pilot trials, Thess-AHALL is in turn an attractive, cost and time effective reliable tool for large companies, SMEs, Start-Ups, research groups and individual researchers contributing to the open character of the LL.
-Open Technology Platform: One of the aims is to develop and test advanced technology for universal access, with the design of innovative interaction paradigms adequate to cope with the peculiar physiological, psychological, emotional, social and ethical factors that influence usability and adoption of technology on the part of elders. Thess-AHALL has already developed, experimented and assessed the user acceptance and friendliness of the devices and applications adopted in the LL [14].

The aforementioned cross-device/application communication framework (CAC-framework http://www.cac-framework.com) also follows the IoT paradigm (publish/subscribe) on top of the web sockets communication [15, 16]. This aligns developments along the Future Internet initiative and project stream, FIWARE, easing the use of generic and specific enablers of FIWARE in the health domain (FI-ADOPT, etc), FIWARE has been adopted and gradually will be supported by the Thess-AHALL infrastructure making the LL more open to developers, products and services, by having the provision incorporating any FIWARE API upon request. Its technological openness continues with the adoption of the open-source UniversAAL platform and its standardized ontologies towards facilitating the implementation of Ambient Intelligence systems.

Finally, members of Thess-AHALL takes part in various H20220 EU projects, significant emphasis is put on the data management and open datasets in collaboration with the Greek chapter of OKFN

(www.okfn.gr). Thess-AHALL strongly supports the principles of publicly available data, data reusability and redistribution. All these in the name of governmental transparency, liberation of social and commercial value and social inclusion and participation.

- Intellectual Property Rights (IPR) principles and Open Innovation: Research and innovation carried out in Thess-AHALL takes place mainly through partnerships regulated by consortium agreements. Thus, IPRs are managed differently according to the consortium negotiation of each project or initiative, guaranteeing free access to the developed tools and solutions, and also allowing openness in the communication and exchange of IP related innovation. IPRs can be negotiated ensuring a subsequent exploitation by all parties. Joint ownership management agreements regulate arrangements where appropriate. When citizens decide to donate their LL participation derivatives (recordings, etc) to the research community, they sign a consent form that they are aware that the derivatives of their participation might be used by researchers for any research purpose.

Resources

In terms of locations, Thess-AHALL is mainly composed of the following points: a) The main Active and Healthy Ageing Living Lab in the **Lab of Medical Physics**, in the Aristotle University of Thessaloniki, b) a replica of the LL in **Chariseio Nursing Home** and c) **5 real homes of elderly people**, containing most of the infrastructure of the LL.

These facilities share a common, minimum infrastructure supporting open standards and open service platform, providing the capacity needed for the pilots to run (see Figure 2).

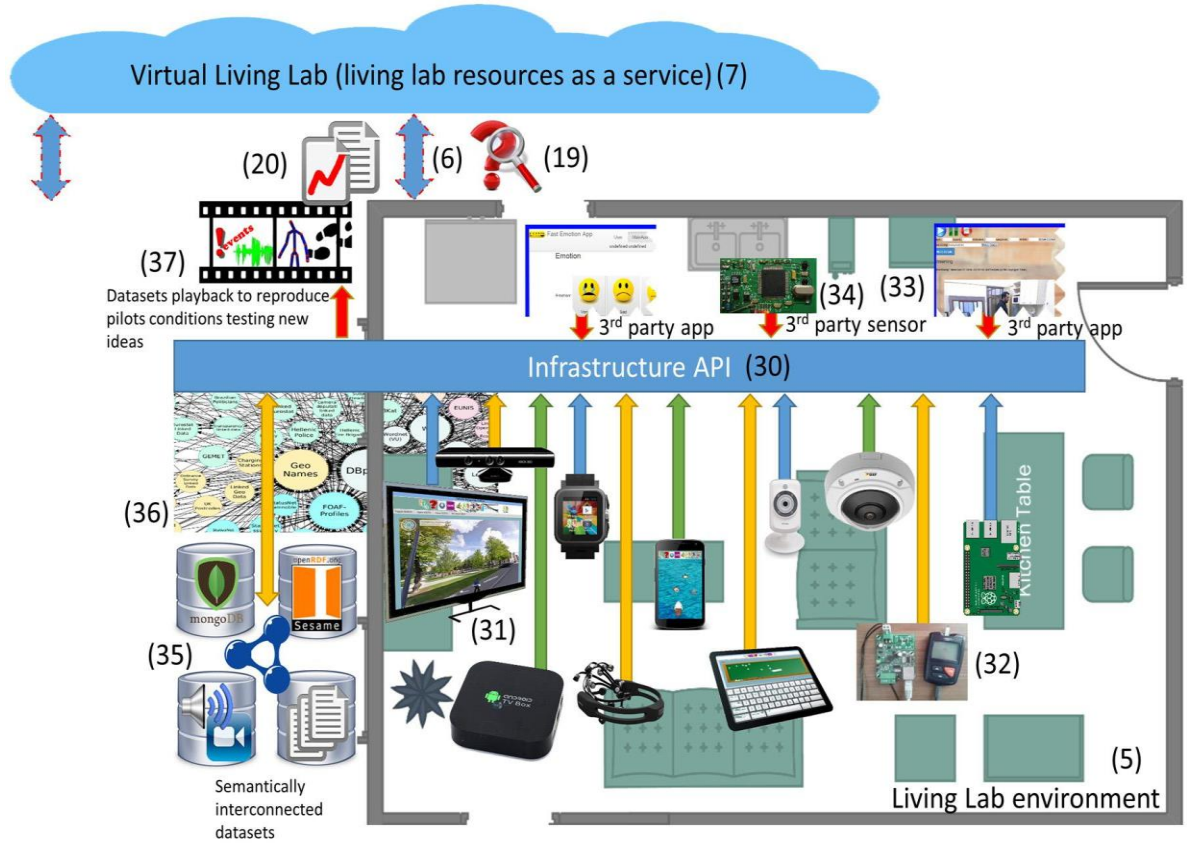

Figure 5. Thess-AHALL technological resources infrastructure: the prototype Living Lab. (5) Living Lab environment, (6) Living Lab Common Middleware, (7) Virtual Living Lab, (19) queries about resources and availability, (20) pilots and evaluation reports, (30) common middleware across the

living labs standardising integration of new applications and services to be tested, (31) Software resources, (32) Hardware resources, (33) Clients' Product/Service "Application", (34) Clients' Product/Service "Sensor", (35) Semantically interconnected datasets, (36) Ontology, (37) Datasets playback to reproducing pilots' conditions

What is selected for the infrastructure of ecologically valid environments represents a wide range of standard infrastructure, scientific and operational procedures adopted by the majority of pilots running across Europe with respect to product/services development for Active and Healthy Ageing. Some of the infrastructure elements[2] are a PC in the role of the "home-gateway" for connection with the servers for data storage, gaming controllers used also for health monitoring (Kinect, Wii Balanceboard, etc) activity trackers and smart watches, blood pressure meters, tablet and smartphones, camera (fisheye and IP), smart mirror and commercial wireless EEG devices. At the application level, recording software, annotation tools, cognitive and physical exercise games as well as communication frameworks are used in the LL. Finally, the support team is producing handbooks describing the approaches and pilot protocols followed within the LL.

Moreover, intensive pilot trials and experimentation during the last 2 years yielded Big datasets stemming from recording the raw information across most of the infrastructure. More specifically, our living lab's datasets, focusing on daily activities, are (from 15 seniors, 104 sessions of 90 minutes): exergame data (already publicly open and linked [12], 1TB database of Kinect in conjunction with Wii Balance Board data, video recordings with face physiological signs extracted, sounds, acceleration from the activity tracker, recordings from the tablet. Additionally, EEG data have also been collected with some of the seniors. Last but not least, continuous recordings of the 5 homes (location c above) allow for a richness of collected data with numerous exploitable uses (see for example Billis et al, 2016b) [8].

Business, finance and expansion

So far, the LL has its own research budget and resources coming from active and ongoing projects. These projects are funded in the European initiatives (FP7, H2020), cross border (Interreg), regional (SME Actions), as well as self-funded projects exploiting and commercializing product/services which matured within the LL (LLMCare - http://www.llmcare.gr).

However, a proper business plan and finance strategy for Thess-AHALL has been built upon and follows the so-called co-piloting concept (Figure 3). According to this, by applying sharing economy concepts in the piloting domain, one or more products/services by different companies can be piloted at the same time, as if they were one unified solution, by real users in ecologically valid environments. The adopting and adapting sharing economy aspect in the pilot trials aims at reducing cost while at the same time improving pilot quality, increasing private funding participation in collaborative innovation projects and ultimately, facilitating the advent of innovative ideas to the market. The cost and time effective pilots act as an incentive for SMEs, startups, small companies and research groups to "try" the Living Lab as a tool for their product and services making them trust it. Thess-AHALL has already adopted this model in the last 2 years by conducting pilots with seniors in its living labs network (http://aha-livinglabs.com/).

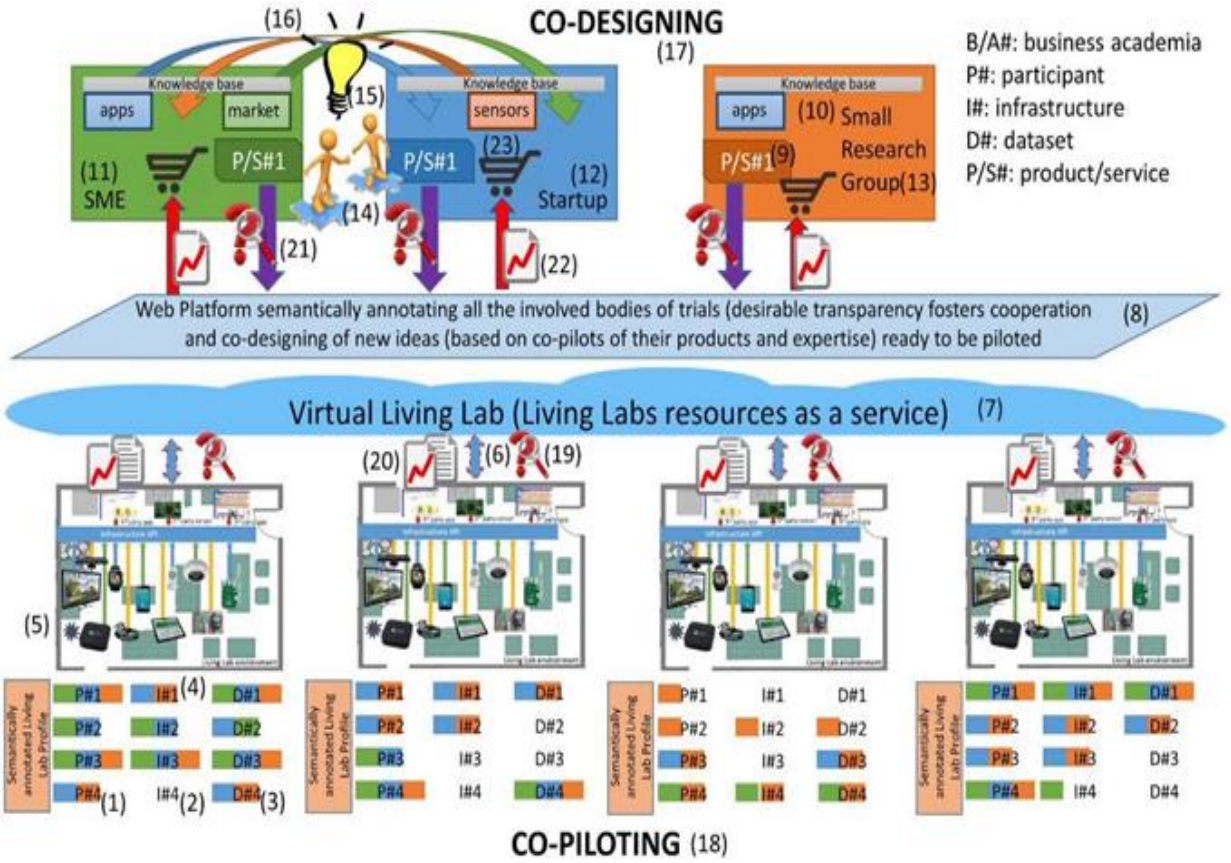

Figure 6. Thess-AHALL business and financing plans are built upon the notion of an envisaged virtual village of living labs and the innovative concept of co-piloting. Illustrated elements of these are: (1) Older participants' profile per Living Lab, (2) Infrastructure per Living Lab, (3) Recorded datasets per Living Lab, (4) Participants and resources per Living Lab, (5) Living Lab environment, (6) Living Lab Common Middleware, (7) Virtual Living Lab, (8) Open Innovation Platform, (9) Product/Service, (10) Expertise/Knowledge, (11) SME, (12) Startup, (13) Small Research Group, (14) Collaboration mechanisms promoting co-designing, facilitating interaction between business and academia and/or between businesses, (15) Facilitating new ideas ready to be piloted, (16) Knowledge transfer and human capital mobility, (17) Co-designing concept, (18) Co-piloting concept, (19) queries about resources and availability, (20) pilots and evaluation reports, (21) Pilot query/request generator, (22) Evaluation Report, (23) Market Go/No-Go decision

Value creation

Thess-AHALL has adopted the co-piloting model for conducting pilots with seniors in its living labs network (http://aha-livinglabs.com/). External research centers express the interest for co-piloting their products since the incorporation of the pilot sites. Research groups within AUTH ask the trials' facilitators to incorporate simple and not time consuming tasks or evaluation tools (questionnaires) in the seniors' activities. The co-piloting process was successful and resulted in a number of publications and outcomes [17]. The LL incorporates lab, healthcare facilities and residential sites, covering multiple use cases where data are collected. The community of committed users is in fact a co-generated asset, since the commitment is pursued through shared projects. Products and services to be tested themselves are in some way co-created and co-designed, since the LL provides access to projects not only with the testing territorial facility and operations management, but also

with AUTH's methodological support and service innovation life cycle advisory. Thess-AHALL has already begun its strategic positioning for cross-border collaborations, widening its network of actors and has the capacity to support the whole lifecycle of the product/service, from the inception and design of the innovative idea to its launching in the market. The above create a set of values for the involved stakeholders, like:

- SMEs: Reduced cost in piloting products in real-life environment with real users, high quality evaluation through pilots, reliable tool underpinning the final go/no-go to market decision, bringing together other parties with complementary expertise as well as co-creation possibilities with experts and users.
- Start-Ups: Find initial customers in the target group, get directly answers whether their idea/prototype/product meets the needs or desires of the customers, reduced cost in piloting prototypes, test and evaluate the product as soon as possible since every market has a lifecycle, and every opportunity thus has a limited window of opportunity before it expires, find synergies with other complementary enterprises, develop a community of early adopters by co-creating and experimenting, be identified and trusted by venture capital.
- Research groups and academia: Find initial participants to test their ideas, run the same pilot (CAC Playback Manager) more than one times to fine tune the product/service/algorithm measuring reproducibility, reduced cost or funding for piloting ideas and research results, find enterprises or startups to adopt their product or research results as part of a bigger solution.
- Venture Capitals: Discover products in piloting phase to invest in, recognize in early stages the acceptability, and indirectly the potential for the product they are going to invest in. Ageing citizens: Interact with a lot of new and innovative ideas which may fit their needs better or suit their lifestyle, be empowered by the process of co-creating solutions that matter to them, becoming an early adopter of innovative solutions, be part of the innovative process.
- Organizations dealing with ageing citizens, caregivers and family members: Empower users to participate in science and technology, contribute to the development (co-creation) of tools tailored to caregivers and family member mitigating effectively the heavy load of caregiving.

Users and Reality

According to participatory design [18], psychologists and researchers are regularly collecting and sharing the user feedback, as well as findings from systematic observation, monitoring and user behaviour analysis in a natural environment. Moreover, being and feeling co-creators rather than just participants in experiments, the seniors provide us with self-monitoring reports of their daily activities (paper and pen). This heavy user involvement distinguishes a LL from any traditional market and user research.

In this context, along with the goal for substantially supporting the design and implementation of useful, usable and acceptable services for the well-being of users, the Thess-AHALL pays special attention to the understanding of the actual needs of the target population, as well as to a clear appreciation of the socio-economic implications of the living-in-place process. Right from the beginning of each project, a rigorous User-Centred, Inclusive Design (UCID) methodology is adopted to identify the practical and psychological impact of technology on users' everyday life and style of interaction. Focus groups and semi-structured interviews during the requirement elicitation, as well

as interaction with the products and services even before the alpha versions (continuing with iterative cycles of participatory design throughout the product's/service's lifecycle) with social assistants, elderly people, families, formal and informal caregivers, Social & Health professionals and local associations, to identify the practical, ethical, sociological and psychological implications of the living-in-place problem and the potential impact of the envisaged assisted living. These target groups jointly take part in the co-design of new products and/or services, in their experimentation.

The participants are recruited by different means, depending on the activity and needs of each project and user profile. Living lab professionals (technologist, psychiatrists, psychotherapists, geriatrists, engineers, occupational therapists, etc.) are responsible for the recruitment of users according to a protocol and an operational plan (work plan, pilot plan, trial plan, etc.). The users & stakeholders are involved in the living lab in different ways, and through a voluntary and informed consent. However, when the LL activities are conducted in the senior's homes, incentives such as long home stay of equipment such as smart TVs, tablets or smartphones are offered. Moreover, strong collaboration with the Greek Association of Alzheimer Disease and Relative Disorders, university hospitals, rehabilitation centres, nursing homes, day care centres for elderly people and municipalities, significantly facilitates these recruitment efforts.

However, fostering the co-piloting approach, efforts for recruitment never stop in order to have a regular and constant visiting flow of elderly people. The involvement in many projects in the AHA domain as pilot partner contributes to this regular visiting of seniors in our Living Lab and in some occasions in their homes. The latter is an example currently followed upon the collaboration with the Parkinson's Association of Northern Greece.

Discussion

As explained and described above, Thess-AHALL may be considered a hub of interconnected pilot sites that enable user-driven innovation in Active & Healthy Ageing and related domains. The main actor of the Living Lab is the Medical Physics laboratory of the School of Medicine at the Aristotle University of Thessaloniki. It emerged in the beginning as a natural way of creating an e-home so as to ease the prospect of seniors becoming aware of technological artefacts and accepting to introduce technologies to their own homes. Joining its forces with ENoLL and its various members, will provide an unprecedented opportunity to extend the existing regional, national and European network of the Living Lab. It will also increase the potential for collaborations and cross-fertilization of ideas. It is also anticipated that the methodological soundness and capacity of the Living Lab with respect to open and user-driven innovation will increase, while it will become possible to integrate best practices and lessons learnt from other success stories of other ENoLL members. The vision is to transform the Living Lab as a wider innovation pole in the Balkan region by developing an engagement policy for the wider territory, in parallel to improving ability to develop and test innovative services and creating synergies with the industrial sector. Strengthening existing synergies with the public sector regarding local and European policies on healthcare, innovation and research, based on user-centered, user-driven data and co-creation schemes, all become key elements of success.

Slowly but surely, Thess-AHALL should start introducing sustainable business models for Living Labs, which will allow for their self-financing. Adherent to this is the idea of enabling the creation of

new business models for SMEs to acquire and test readily available datasets at minimal cost, facilitating business and knowledge growth, while matching supply and demand of ideas between AHA stakeholders (senior citizens, carers, nursing homes, patient organizations) and SMEs or academia.

The hand-shaking with the Open Knowledge Foundation local chapter supports the activities of Thess-AHALL significantly towards openness, such as open access to data produced within Living Labs thereby facilitating open (clinical) trials, in specific. Inherent contributions to data management planning will increase the access to research data produced with field trials with end-users. In that context, the interchange with other ENoLL thematic networks and Working Groups, would strongly enrich the activity lists towards studies of well-being and health, smart cities, future internet and internet of things, as well as, social innovation and social inclusion.

To conclude, the aim of this paper was to illustrate the process of founding the living lab in Thessaloniki [19] and systematically describe how it complied with guidelines of the ENoLL network, thereby expanding its services by enabling co-creation in a sustainable, open and innovative way. This compliance exercise is deemed useful and may well serve as a guide and reference for any similar endeavor.

All authors declare that they have no conflicts of interest

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Reversible and irreversible dementias with psychosis as first presentation: Our experience from the clinical practice

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Abstract

There are types of dementia, either reversible or irreversible, presenting with psychosis. In such cases there is a possibility to misdiagnose dementia as psychiatric disorder. Herein, we highlight 5 cases from our daily clinical practice which could be misdiagnosed because of a prevalent psychotic sympomatology. After a careful differential diagnosis and specific treatment dementia was reversed, while irreversible dementias remain unchanged. No doubt we should always exclude reversible causes of dementia before attributing the symptoms to psychosis.

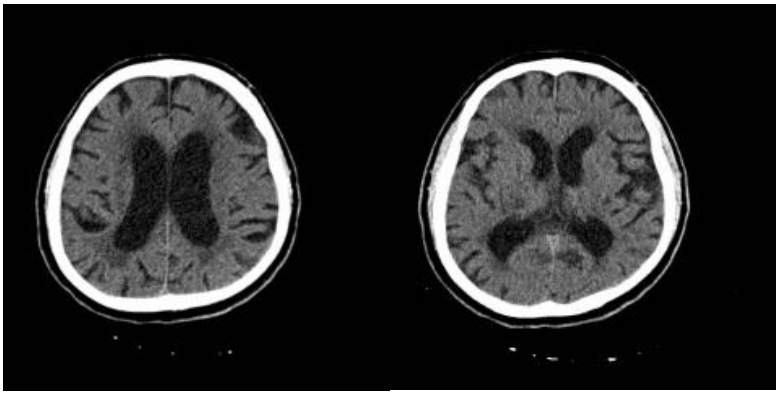
Keywords: Reversible and irreversible dementia - Psychosis

Introduction

Dementia is a common neurological disease characterized by insidious onset with high social and economic impacts. The subtle and variable emergence of dementia symptoms makes recognition of the syndrome problematic. Furthermore, when the presenting symptoms reminiscent a psychosis there is a possibility to misdiagnose these patients. It's crucial to differentiate neuropsychiatric symptoms such as agitation, aggression, delusions, hallucinations, disinhibition and depression as a part of dementia or as a part of psychiatric disorder [1]. If we want to differentiate a psychiatric disorder from dementia we should keep in mind that almost all of the psychiatric symptoms could be met in dementia and that till now there are no criteria or specific signs that can lead to a safe differential diagnosis. Most frequently disorders of mood and behavior like depression, agitation or psychosis are reported in dementia but mania, obsessive-compulsive disorder or addiction to alcohol met only rarely [2].

Case number 1

A 69- year –old retired policeman was referred as 12-month history of progressive behavioral changes. He initially got divorce with no apparently reason from his wife and moved in another city where he got married again. His new wife and also his son mentioned that from one side he got angry very easily and wanted all the time to have right, and on the other hand he became less affective and empathic towards his family. At this time he was diagnosed with depression and prescribed SSRIs. One year later he developed compulsive-obsessive behavior with microbiophobia. At the same time he became hyperemotional and burst into tears many times every day. Furthermore, he changed his eating habits by eating large amounts of food, especially sweets (hyperorality). His speech was slow, with halts between the words, and omissions of grammar. His neurological examination was unremarkable and his neuropsychological tests revealed predominantly executive impairment. His brain CT showed volume loss at the frontal and anterior temporal lobes. Finally he was diagnosed with frontotemporal dementia and his behavioral abnormalities managed with low doses of atypical antipsychotics and SSRIs.

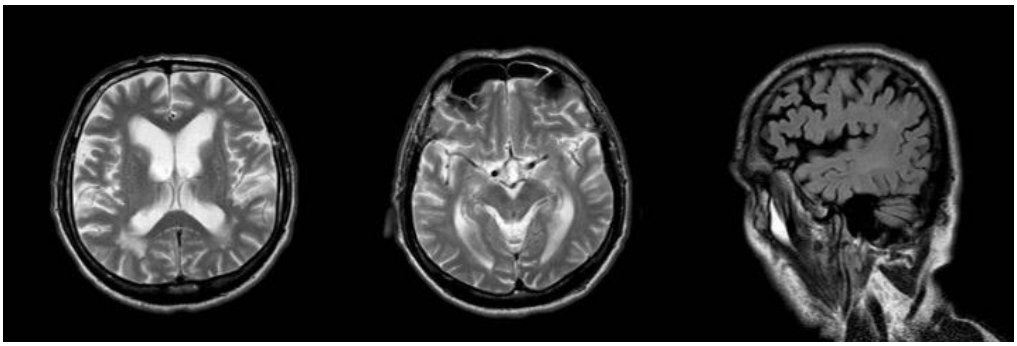


Case number 2

A 52-year-old man with mild mental retardation who was characterized by his family as a ‘’gentle soul, loved by everyone” had out of the blue a severe psychomotor excitation. For that reason low dose of haloperidol was administrated intramuscularly, and unexpectedly he developed severe rigidity with oculogyric crisis. As long as he remained at the clinic, he had recurrent visual hallucinations (a ghost chased after him and caught him) and fluctuations in cognition and his level of alertness with episodes appeared like he blank out or had speech arrest. The neurological examination consisted of visuospatial dysfunction with good memory and attention and from his history rapid eye movement disorder sleep behavior revealed, referring at least to the two previous years. He diagnosed as probable Lewy body dementia and low doses of aripiprazole prescribed with caution. Note that the acute development of psychiatric disorders in Lewy body dementia is extremely rare, but is not impossible.

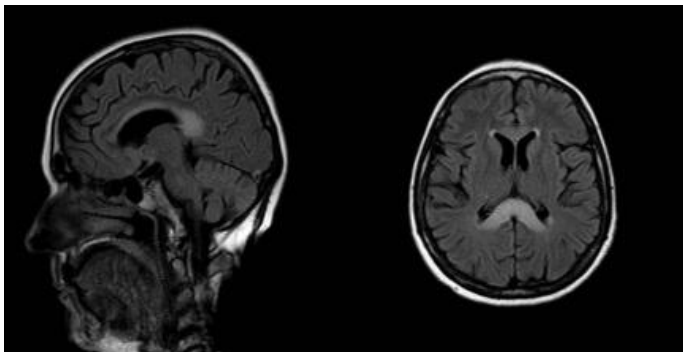
Case number 3

A 60-year-old man, owner of a security company, referred due to behavioral changes the last six months. His wife described hyper sexuality and delirium of jealousy. He was diagnosed with depression and prescribed SSRIs but the next months his symptoms deteriorated and he also reported frustration at work and difficulties dealing with everyday duties. His family underlined his decline to interfere with daily activities. In more detail he became confused about payments, he forgot many of his appointments, he got lost while driving to his customer's houses and his ability at work decreased. He suffered from insomnia. Mini mental score test was 22/30 and MOCA test score 21/30 and he also had low levels of amyloid beta 1-42 protein, along with high levels of total tau and elevated phosphorylated tau 181 at the spinal fluid. MRI scan of the brain revealed brain atrophy. As far as he was diagnosed with Alzheimer disease he started medication with cholinesterase inhibitors.



Case number 4

A 52-year-old teacher developed addiction to alcohol and didn't take care of her nutrition. She had no past psychiatric history and she was prescribed only supplementary medication for vitamin B_{12} deficiency. The last two years she had gradually deteriorated memory problems and finally she was unable to teach. She suffered from glossitis, cheilitis and dermatitis. She was referred to ER department due to delirium with paranoid ideas of conspiracy. She manifested excessive and often incoherent talkativeness (logorrhea) and flight of thoughts (ideorrhea). She insisted on being blind and accused doctors for that. MMSE was 22/30, laboratory exams showed elevated transaminases and decreased niacin and her MRI revealed demyelination at the splenium of corpus callosum. This is a case of pseudo-dementia due to pellagra and Marchiafava -Bignami disease.



Case number 5

A 62 -year-old housekeeper with a past medical history of high blood pressure was referred as a 5-month history of memory problems, difficulty in concentration and inability to take care of the house. She had visual and auditory hallucinations (she was looking for her lost baby and a voice asked her to breastfeed her baby) and she used to walk in the neighborhood aimlessly. She was firstly diagnosed as Alzheimer disease and was prescribed rivastigmine, but her symptoms continued to deteriorate. She was reevaluated and extensive laboratory and imaging studies including lumbar puncture, brain MRI, and EEG, were unremarkable. Finally, she was diagnosed as pseudo-dementia due to Ganser syndrome. It was characteristic that during examination, she was frequently gave an incorrect answer that showed some understanding of the subject and possible knowledge of the correct answer. For instance, when she was asked about the color of the sky the answer was yellow. Her symptoms mentioned in conjunction with a marked psychosocial stressor (family arguments). Cholinesterase inhibitors were stopped and she fully recovered after supportive psychotherapy and administration of SSRIs.

Discussion

Detailed medical history with information about patient's medication, family history, trauma, past psychiatric and other medical history is fundamental, as long as the careful evaluation of even subtle changes in functional ability and the recognition of new symptoms. Therefore, patients should be assessed periodically. Interview of the family members and care givers is recommended, keeping in mind that these patients try to hide their symptoms. Laboratory tests, brain magnetic resonance imaging, electroencephalogram and CSF analysis are necessary to identify or rule out secondary causes of dementia and coexisting disorders [3].

Although there are not guidelines or standard algorithms to differentiate neuropsychiatric symptoms of dementia from psychiatric disorders some rules may be helpful [4]. For example, in depression cases the onset is usually easy to be determined (e.g. the patient says that my symptoms begun on May of 2016) with rapid progression, in comparison with dementia (e.g. the patient says that my symptoms begun sometime last summer), where no deterioration is noticed. In psychosis predominate not only the visual, as do in dementia, but also the auditory hallucinations which are more strange and organized, without medication no remission of hallucinations is recorded and suicidal thoughts are common in psychiatric patients in contrast with the patients suffering from dementia [5].

The authors declare that they have no conflicts of interest.

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Language performance: an indicative marker for subtle changes in MCI subtypes

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Abstract

This study aims at investigating morhpo-syntactic variables perception by MCI subtypes patients beyond memory impairment. Novel language tasks have been introduced and conducted in a computerized environment in order to prove language as a sensitive indicator of MCI. In the present study 40 amnestic MCI single domain (aMCI-SD), 53 amnestic type of multiple domain, (aMCI-MD) and 22 healthy controls (HC) have been recruited. Linguistic activities processing has been correlated to well established neuropsychological tests and language exercises granted. Statistically significant differences were found by non-parametric tests (One-way ANOVA on ranks) with p = .05 in the scores of sentence and word -level tasks that required the perception of different morpho-syntactic variables (verb aspect, tense etc.) and p=.012 in the durations of the above tasks (time needed to complete the tasks). More specifically, more time was needed for the aMCI-MD than the HC. In conclusion, the systematic use of language in diagnostic computing environments could play a critical role in complementing the cognitive profile of the elderly with different subtypes of the MCI.

Keywords: Mild Cognitive Impairment – Language - Cognitive function – Amnestic - Computerized environment

Introduction

Mild Cognitive Impairment (MCI) subtypes have been defined according to their neuropsychological profile that entails memory and non-memory deficits. According to research and clinical practice, despite cognitive change MCI subtypes patients present heterogeneity, thus there is still need for a consensus about distinct cognitive profiles and MCI classification. The Amnestic MCI multiple domain subtype (aMCI-MD) is considered of higher risk to progress to AD compared to Amnestic single-domain MCI subtype (aMCI-SD) [1]. Research has emphasized on memory deficits, while recent research highlights the predictive value of language performance to define screening and

intervention methods for MCI. More specifically, research indicated difficulties in discourse comprehension general for the MCI groups [2]. However language exploitation concerning also morpho-syntactic capacity is challenging in order to investigate subtle cognitive changes in varying groups of MCI.

According to Petersen criteria [3], beyond the clinical subtype's existence, a variety of multiple degenerative etiologies are linked to each MCI subtype. Several cohorts define different criteria for MCI [4-6]. Nonehteless, despite the different classification criteria that exist, there is a consensus that MCI refers to persons: a. with no dementia, b. measurable cognitive deficits c. a clinical syndrome with high risk of progression to dementia.

Clinical praxis and research have identified two subtypes of aMCI, according to the cognitive domains that are affected: single-domain (aMCI-SD) and multiple-domain (aMCI-MD) sub-types and correspondingly non amnestic, single or multiple domains [7].

Among the MCI subtypes patients (Figure 1), the aMCI subtype is affected by early episodic memory impairment and naming difficulty, while the likelihood to progress to Alzheimer's disease is higher [8]. More specifically the rate of aMCI conversion to AD is 10% to 15% per year, while healthy controls (HC) are expected to progress at a rate of 1% to 2% per year [9].

Also, the define characteristics of aMCI is episodic memory and delayed recall [10]. Moreover language ability has been assessed in the aMCI subgroup according to letter and category fluency indicating poorer performance in verbal fluency compared to aMCI-SD [11]. In recent studies the aMCI subgroups present naming difficulty and abstract word definition ability [12].

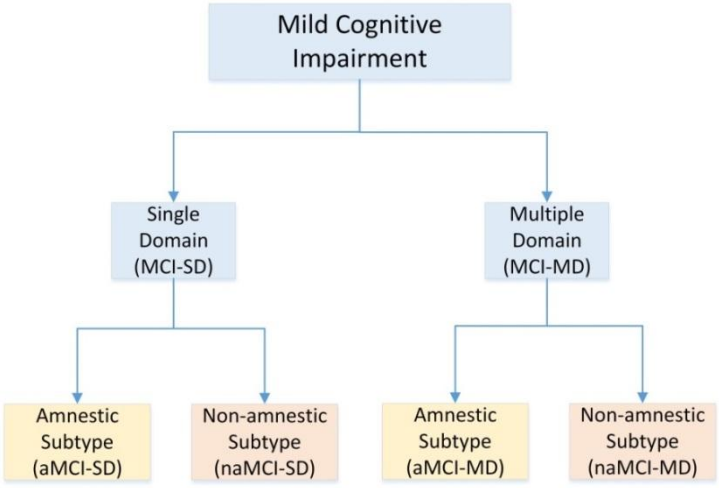

Figure 1. Sub-divisions of Mild Cognitive Impairment subtypes

Beyond the semantic deficits in aMCI subgroup identified in linguistic tasks, morpho-syntactic processing, sentence structure perception and binding into a coherent meaning has been so far assessed mainly according to aging changes [13] and in the early stage of dementia [14]. Lexical - syntactic processing in MCI subtypes patients and subtle changes among MCI sub-categories remain unexplored. Deficits in words' formation according to their grammatical and syntactical role have to be further assessed in MCI subtypes.

Therefore, more information about the capacity of MCI subtypes patients to perceive the dynamic role of morpho-syntactic and verb argument structure may complete their profiles according to a critical cognitive domain as language. Moreover, as it is known linguistic abilities are correlated to

cognitive skills as attention and executive function [15].

The main aim of the current study was to investigate the morphosyntactic ability of MCI subgroups and strengthen the hypothesis that the aMCI-MD entity presents more deficits vs aMCI-SD in specific cognitive domains as language, attention, executive function and visuospatial ability. Therefore the aMCI-MD subtype could be a precursor of dementia [1].

Subjects and Methods

The pilot study was hosted in the Alzheimer's Day Care Unit "Saint John" in Thessaloniki, Greece, (October, 2016) and all procedures were performed in agreement with ethical protocols approved by the hosted institute with the ethical approval number (Pr Nr.: 170 /2016 AI, September, 2016). The criteria for participant's recruitment (of all user groups) are presented in Table 1. The proposed linguistic tests were applied to three age and education-matched groups: 40 amnestic MCI single-domain (aMCI-SD), 53 amnestic type of multiple domain, (aMCI-MD) and 22 healthy controls (HC).

Table 1. *Inclusion and Exclusion criteria*

Inclusion Criteria	**Description**
Age	All subjects had to be over 55 years old
Computer Driving Abilities	This was a self-administered test, so users had to be able to use the computer on their own*
Neuropsychological tests	A positive diagnosis was required for people with MCI, while a negative diagnosis was required for controls
Language skills	Native speakers and people with proven fluency in Greek language (both in written and oral)
Exclusion Criteria	**Description**
Age	People over 85 years old
Computer Driving Abilities	People with no proven ability to give the computerized test were excluded from this study
Neuropsychological tests	People who already had progressed to Mild Dementia
Depression	People with severe or untreated depression (untreated depression (Geriatric Depression Scale-GDS ≥ 5)
Stress (untreated anxiety)	High level of stress may cause noisy results
Vision/Acoustic Problems	People with vision and/or severe acoustic problems not corrected at the time of the test
Other medical exclusion criteria	psychotic traits, behavioral problems, neurological disorders, many ischemic lesions, antipsychotics, Cholinesterase inhibitors, sensory deficits

Before the pilot realization participants received standard neuropsychological assessment,

including the Mini-Mental State Examination test (MMSE) [16], the Trail Making Test-Part B (TMT-B) [17] and the Verbal Fluency Test (FAS) [18]. The aforementioned neuropsychological tests have been used in order to assess: a. general cognitive status b. executive ability and c. verbal fluency, particularly of the a-MCI group. The Trail Making Test-B was included for mental flexibility assessment required by everyday language performance monitoring (higher-order cognitive ability) [19]. As a group, the standard neuropsychological test results as well as personal interview by neurologists were used to sense the MCI condition in advance (ground truth).

Table 2. *Description of participants and neuropsychological test results*

Parameters	Groups of participants			
	Controls	*a-MCI-SD*	*a-MCI-MD*	*Kruskal-Wallis H test*
N	22	40	53	-
Sex M/F	2/20	5/35	9/44	$\chi^2(2) = .010$ ($p = .014$)
Age (in years)	65.95 (SD = 6.18)	68.22 (SD = 5.51)	72.43 (SD = 6.62)	$\chi^2(2) = 5.531$ ($p = .063$)
Education (in years)	10.00 (SD = 3.74)	12.08 (SD = 4.37)	10.77 (SD = 4.74)	$\chi^2(2) = 1.671$ ($p = .434$)
MMSE	29.13 (SD = 1.14)	28.91 (SD = 1.02)	27.22 (SD = 2.07)	$\chi^2(2) = 16.883$ ($p < .001$)
TMT-B	134.92 (SD = 40.46)	161.39 (SD = 44.47)	236.50 (SD = 99.33)	$\chi^2(2) = 19.946$ ($p < .001$)
FAS	11.44 (SD = 2.85)	12.87 (SD = 2.65)	10.25 (SD = 2.99)	$\chi^2(2) = 9.418$ ($p < .009$)

Within the current study we exploited the role of language in accordance with other cognitive functions to understand better MCI subtypes patient's cognitive profiles.

Previous research has investigated sentence tasks in relation to the ability of patients to understand words' relations [20]. Among other factors, syntactic comprehension deficits have been indicated as a linguistic marker for MCI diagnosis [21]. Based on this research background, novel language tasks have been designed and implemented in a fully computerized environment to investigate language subtle deficits of MCI subtypes patients in micro-linguistic level. Participants had to reconstruct sentences or construct words by applying morphological and syntactical rules in order to provide comprehensible sentences.

More specifically, the two linguistic tasks were designed on the basis of verbs' inflected morphemes (verbs' aspect, person, number, voice etc.) and the role of grammatical components (conjunctions, adverbs).

The first task is targeted to assess syntactic priming which entails per se executive functions. A number of words were presented in a random order and participants had to construct syntactically correct sentences under a number of distracting factors for instance unused words and duplicates

words in different tense.

The second task demanded a number of different procedures including determination of tense and number, interpretation of pronouns and prepositions to fill in gaps and sentences. For the successful completion of words according to their semantic and syntactic features participants had to comprehend word order and subject-object relations.

In general, we aimed to comprehend thoroughly MCI subgroups cognitive deficits though language processing. The proposed language tasks were designed to further exploit the perception ability of morpho-syntactic relations and dynamic changes of micro variables (e.g. verbs') by MCI subgroups in order to structure meaningful phrases as verb phrases.

Results

The statistical analysis was conducted using SPSS v21.0 (IBM Corp., Armork, NY) statistical software. Results indicated statistically significant differences in the mean scores of participants during the performance of the morpho-syntactic tasks among the study groups: a. the control group (CG), b. the single domain (aMCI-SC) and c. the multiple domain groups (aMCI-MD). The two test metrics used in this study were the rate of the correct responses and the total duration for linguistic tasks completion (Figure 2).

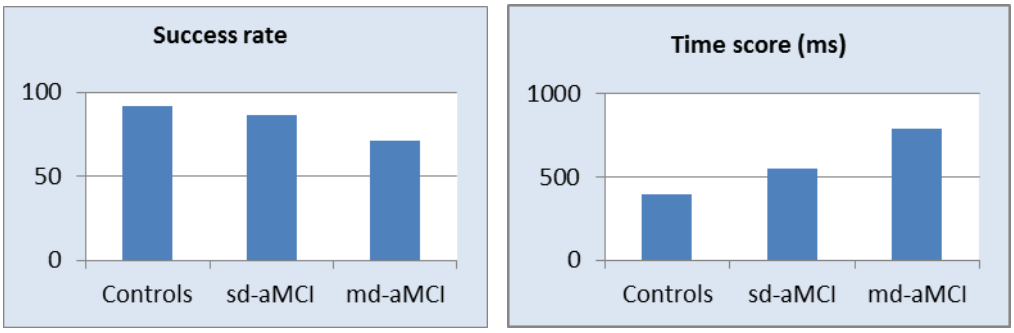

Figure 2. Success rate and linguistic tasks duration

The Shapiro-Wilk test of normality for the variables of score and duration was significant ($p < .001$ in both cases, so we followed a non-parametric test for the comparison of the means in the three groups of participants (One-way ANOVA on ranks or Kruskal-Wallis H test). The results indicated that there is a significant difference in the median scores x^2 (2, N = 115) = 5.659, p = .05 and the median durations x^2 (2, N = 115) = 8.929, p = .012 among the three study groups.

On the other hand, the results of the Mann-Whitney test provided evidence that the CG group had statistically significant differences both in test scores (U = 131, p = .004) and durations (U = 115, p = .001).

Positive correlations of the score results with the scores of the applied neuropsychological tests were found in the sample, indicatively with the MMSE (r = .337, p = .018) and the TMT-B (r = -.346, p = .015). Similarly, the durations were found correlated with the MMSE scores with (r = -.304, p = .034) and the TMT-B (r = -.294, p = .041). To be noted that correlations with the FAS test were not found. No in-group correlations were found between the performance of the participants in the language tasks and the other standard neuropsychological tests (Table 3). But the two metrics used in this study, the score and duration were found to be correlated with each other in the MCI

subgroups and in total.

By examining the scores and the relationships between the two subtasks, it was found that the controls and the aMCI-SD groups performed better in sentence structure and word formation tasks as indicated in the Figure 3.

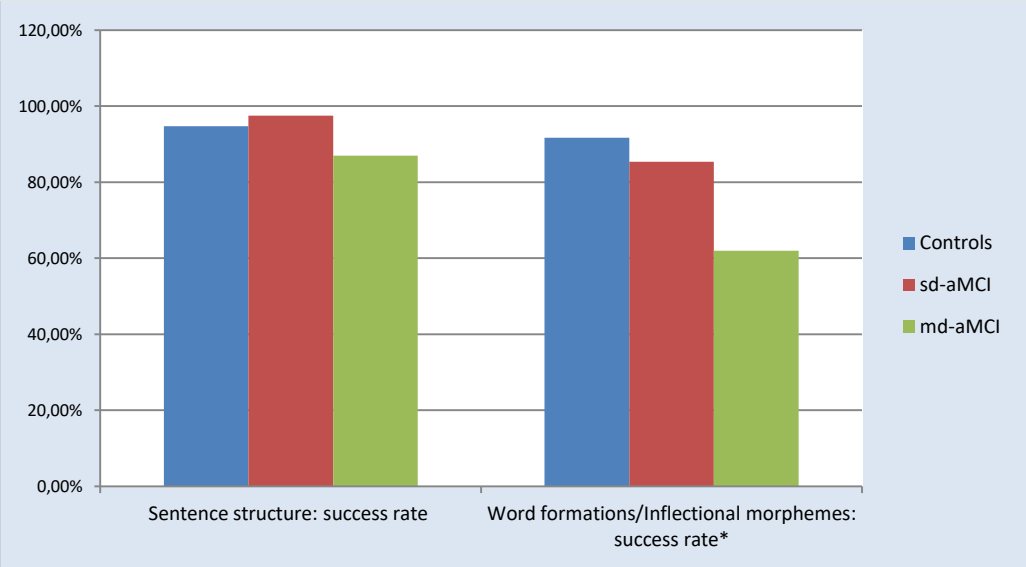

Figure 3. Average difference between tasks

Moreover, the two performance metrics were tested for their in-between correlation. It was found that those two were strongly correlated with r = -.627, p < .001. Within control group no statistically significant correlations were found, but within the single domain (r = -.596, p = .002) and the multiple domain (r = -.671, p = .006) it was found statistically significant correlations at the .001 level.

Table 3. *Correlations between language test results and to other standard neuropsychological tests per user group and in total*

Tasks results	Neuropsychological tests results				
	MMSE	*TMT-B*	*FAS*	*Scores*	*Durations*
All Cases					
Scores	r = .337* (p < .018)	r = -.346* (p = .015)	r = .218 (p = .151)	1	r = -.627** (p < .001)
Durations	r = - .304* (p = .034)	r = .294* (p = .041)	r = -.230 (p = .128)	r = -.627** (p < .001)	1
Select Cases: Control Group					
Scores	r = .518 (p = .125)	r = .076 (p = .835)	r = -.113 (p = .831)	1	r = -.070 (p = .805)
Durations	r = -.050 (p = .892)	r = -.407 (p = .243)	r = -.241 (p = .646)	r = -.070 (p = .805)	1
Select Cases: aMCI-SD					

Scores	r = -.034	r = -.322	r = -.246	1	r = -.596**
	(p = .876)	(p = .125)	(p = .247)		(p = .002)
Durations	r = -.096	r = .317	r = -.488*	r = -.596**	1
	(p = .656)	(p = .131)	(p = .016)	(p = .002)	
Select Cases: aMCI-MD					
Scores	r = .391	r = -.107	r = -.264	1	r = -.671**
	(p = .149)	(p = .705)	(p = .342)		(p = .006)
Durations	r = -.364	r = .067	r = -.064	r = -.671**	1
	(p = .183)	(p = .813)	(p = .820)	(p = .006)	

Discussion

Within the present study, morpho-syntactic capacity of MCI subtypes patient's has been emphasized. More specifically, syntactic abilities are evidenced as relatively well reserved at MCI individuals. Tests' results were also confirmed by other studies concerning syntactic abilities of MCI and AD [22]. Recent research documented that morphological and syntactic information could be a good predictor of MCI syndrome [23]. Moreover, the ability to analyze mentally the correct syntactic structures requires beyond syntactic and grammatical rules' recall, cognitive abilities highly related to word's formation as attention and executive function [24].

However, so far research investigated language processing of MCI individuals in morphological and syntactical level mainly on the basis of spontaneous speech production [25]. Another study explored the abilities of HC and aMCI-MD individuals [26] to indicate the predictive validity of sentence comprehension. Nonetheless, language functions are variably affected in MCI subtypes patients' and this variability hasn't been thoroughly exploited.

In this line, the present study pointed out that the perception ability of grammatical components in words' formation in sentence level could be having good discrimination ability in different subtypes of MCI. Future plans include a test-retest reliability analysis and the use of the proposed tasks for MCI conditions monitoring.

Limitations and future research

Within the present study some initial proofs has been provided regarding the discriminating ability of the proposed linguistic tasks to sense the MCI condition. A future test –retest study under the same conditions and using the same content will prove the repeatability of the proposed test as a complementary MCI monitoring and diagnosis method.

All authors declare that they have no conflicts of interest.

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Diabetes and obesity in Alzheimer's disease: common mechanisms and potential links

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Abstract

Alzheimer's disease (AD) is a degenerative disorder of the central nervous system associated with extensive loss of neuronal cells, and characterized clinically by progressive loss of memory, cognition and emotional stability, that leads to profound mental deterioration. Despite vigorous efforts in the field, AD pathogenesis is still not fully understood. Recently, a number of risk factors that may shed light on the molecular mechanisms underlying the development of the diseases have been identified. Among these factors, obesity and diabetes mellitus (DM) are increasingly gaining importance, mainly due to results of several studies suggesting that they may exacerbate conditions hypothesized to promote AD. Although the precise mechanisms of their association with impairment of cognitive performance remain to be elucidated, the adverse effect that these disorders exert on the aging brain could be hindered by alterations in several molecular, metabolic and hormonal pathways, including defects in insulin signaling and glucose metabolism. The present review reinforces the notion that DM and obesity are strongly associated with multiple deviations from the proper functioning of the brain, by focusing on possible links between these disorders and AD. These include, among others, glucose metabolism and insulin signaling abnormalities, variations in energy expenditure, changes in adipokine levels, promotion of b-amyloidogenesis, and induction of oxidative stress. Therapeutic approaches focused on preventing or handling obesity and insulin abnormalities may be of therapeutic benefit for adults with age-related memory impairment and AD.

Keywords: Alzheimer's disease - Risk factors – Obesity - Diabetes mellitus

Introduction

Life expectancy has increased dramatically over the past century, particularly in industrialized countries. This rapid and unprecedented increase was associated with profound changes in the prevailing patterns of disease and morbidity, just as health-threatening conditions associated with ageing are becoming more and more prominent. Aging, a long thought inexorable road towards vulnerability and multisystem physical and functional decline is related with a wide range of human disorders, including DM, obesity, and neurodegenerative diseases.

AD, the most prevalent form of dementia, affects 20 to 30 million individuals worldwide and its incidence is expected to quadruple over the next 50 year [1]. It is an age-related disorder of the central nervous system characterized by deposition of senile plaques and neurofibrillary tangles in

the brain accompanied by synaptic dysfunction and neurodegeneration [2]. The clinical appearance of AD, manifested by brain atrophy and hypometabolism, is predominated by severe cognitive impairment [3], with symptoms gradually progressing from episodic memory problems to a global decline of cognitive function that leaves patients with end-stage AD bedridden and dependent on custodial care. In most cases, death occurs on average of 9 years after the disease diagnosis. Genetic and environmental factors can determine one's risk for AD [4] and an in depth understanding of how these risk factors modify the amyloid cascade is vital for the development of targeted interventions for AD prevention and treatment. Here, we will discuss recent hypotheses concerning the common mechanisms associating onset and progression of AD with DM and obesity.

Materials and Methods

This systematic review aimed to include published research, clinical and epidemiological studies that examined the association of AD with DM and/or obesity and that met the following inclusion criteria: (1) the study was published after 1990, (2) addressed at least two of the aforementioned comorbidities and their potential links, and (3) used well-established protocols to assess their outcomes.

PubMed and bibliographies were used to identify relevant papers. The keywords used were: diabetes, glucose metabolism, insulin dysregulation, metabolic syndrome, obesity, overweight and adipokines in combination with the terms cognitive, oxidative stress or AD, in full or truncated versions. Potentially eligible scientific publications were collected in full-text versions, after scanning titles and abstracts.

Diabetes Melitus and Alzheimer's disease

Corroborating evidence suggest that phenotypes associated with alterations on insulin homeostasis are at increased risk for developing dementia. These phenotypes involve prediabetes, DM, metabolic syndrome and obesity [5]. DM is one of the fastest growing epidemics of modern times. As the fourth leading cause of mortality, it affects 250 million people worldwide and accounts for 3 million deaths annually [6]. In recent years, significantly more interest has been dedicated to the effect of DM on the brain and its implication in the development of neurological comorbidities. Both types 1 (T1DM) and 2 DM (T2DM) are important risk factors for decreased performance in several neuropsychological functions. As expected, however, the specific deficits in cognitive abilities between the two types do not completely overlap.

Decline of cognitive function in Type I and II diabetes melitus

Neuropsychological studies have shown that patients with T1DM perform noticeably poorly on several cognitive functions evolving the rate of information processing, attention, mental flexibility, and visual perception [7]. In patients with T2DM memory, psychomotor speed and frontal lobe/executive function seem to be mainly affected [8]. Table 1 summarizes the global and specific subtypes of cognitive dysfunction in T1DM and T2DM [9].

Table 1. *Summary of cognitive functions found to be affected in T1DM and T2DM*

Cognitive Functions	T1DM	T2DM
Verbal memory	↓	↓
Non verbal memory	↓	↓*
Attention	↓*	↓
Processing Speed	↓*	↓*
Visuospatial performance	↓*	-
Psychomotor efficiency	↓*	↓

↓: decreased; − does not seem to be affected or evidence lacking. Note: domains marked by asterisks have particularly strong supporting data.

T2DM, a disorder primarily defined by chronic hyperglycaemia, is also associated with higher risk of AD. In T2DM pre-clinical syndrome, hyperinsulinaemia precedes hyperglycemia by many years and as a result chronic over-stimulation leads to insensitivity of the insulin receptor or defect of signal transduction which is considered to be the cause of the disease [10]. Upon the onset of T2DM, hyperinsulinaemia is present among most of the diagnosed cases [6]. Chronic hyperglycemia and hyperinsulinemia enhance advanced glucose end products (AGEs) formation [11], which results in an overproduction of reactive oxygen species (ROS) [12]. There are also several other factors by which DM increase the risk of AD. Nevertheless, the most attention is retained by the ones linked to insulin, briefly described below.

Insulin dysregulation and neurodegenerative disease: shared and specific mechanisms

The regulation of insulin action and glucose metabolism is an extremely complex process that requires synchronized communication among various systems and integration of biochemical, hormonal, and neurogenic signals. The occurrence of abnormal levels of glucose, the main energy substrate of the human brain, may have devastating effects on its normal function [13]. It is widely recognized that prolonged and severe hypoglycemia besides acutely affecting cognition, mood, and conscious level, may lead to permanent brain damage [14]. On the other hand, the deleterious effects of hyperglycemia are mediated through an increased flux of glucose through the polyol and hexosamine pathways [11], disturbances of intracellular messenger pathways and an imbalance in the generation and scavenging of ROS [15].

Investigation of the contribution of peripheral glucoregulation in AD, has demonstrated that glucose uptake and utilization in the brain is reduced in AD patients. The extent and regional location of glucose hypometabolism correlate with the severity of symptoms. Furthermore, increasing evidence suggests that reductions in glucose utilization occur at the presymptomatic stages of AD and can be observed before the onset of disease [16, 17]. Early studies demonstrated that AD patients with impaired glucose tolerance respond to glucose challenge and reduced insulin-mediated glucose uptake with high insulin levels. This pattern is characteristic of insulin resistance. Although insulin does not seem to influence basal cerebral glucose metabolism or transport of glucose into the brain, evidence suggests regionally specific effects on glucose metabolism [18]. The effects

discussed so far focused on peripheral glucose metabolism. However, there are several other mechanisms that may plausibly contribute to insulin-mediated memory deficits and reduced performance in multiple domains of cognition (see Table 2).

Table 2: Insulin-related mechanisms shared by neurodegenerative disorders

Decreased cerebral glucose metabolism
Increased inflammation
Increased oxidative stress
Increased advanced glycation end products
Synaptic dysfunction
Decreased neurogenesis

The presence of insulin receptors (IRs) in synapses on astrocytes and neurons [19, 20] as well as their selective localization in the hippocampus and medial temporal cortex imply insulin's involvement in functions far removed from its role in the mediation of glucose uptake [21,22]. Indeed, insulin exerts multiple effects in the brain, consisting of neuromodulatory, neurotrophic and neuroendocrine actions [23]. Abundant evidence suggests a key role of IRs in the modulation of synaptic activity through regulating the release and uptake of neurotransmitters, such as acetylcholine [24], norepinephrine, and dopamine [25]. Data from recent clinical and neuropathological studies support the notion that a defect in insulin metabolism accompanied by a reduction in insulin levels and insulin receptor expression [26], as well as a deficient downstream signaling pathway may be linked to verbal and memory decrements [27]. In physiological conditions, insulin receptors are present at synapses, and phosphorylation of the IRs and Akt, which reflects proper insulin signaling, is linked to presence of GluA1 and GluN2B favoring synapse function and memory formation [28]. Pathological conditions (e.g., DM, AD), associated with decreased levels of expression and phosphorylation of IRs are subsequently linked to decreased levels of GluN2B and GluA1 at synapses. Reduced insulin signaling ultimately leads to impaired synapse plasticity and function [29].

Another common molecular pathology shared by DM and AD is the elevated AGEs levels and the related oxidative stress. Finally, insulin has long been known to play a part in peripheral response to inflammation, a critical promoter of AD pathogenesis [30]. Especially during long-term hyperinsulinaemia or chronic inflammation, insulin may aggravate the inflammatory response and increase markers of oxidative stress [31].

Insulin, Insulin-degrading enzyme and amyloid deposition

According to recent studies insulin is implicated in the metabolism of the proteins Aβ and tau, which are considered as the main constituents of the characteristic neuropathological lesions in AD. Despite insulin's role as a neurotrophic factor at moderate concentrations, extensive presence in the brain is associated with reduced amyloid-β (Aβ) clearance due to competition for their common and principal depurative mechanism - the Insulin-Degrading Enzyme (IDE) [32]. IDE is a metalloprotease responsible for the catabolism of insulin and Aβ, and is suggested to play a critical role in Aβ clearance in brain. Insulin can regulate IDE expression, as well as directly compete with Aβ for binding to IDE. Since IDE displays a higher affinity for insulin than for Aβ, brain hyperinsulinism may deprive Aβ of its main clearance mechanism [33]. Hyperglycemia and hyperinsulinemia seem to accelerate brain aging also by inducing tau hyperphorylation and amyloid oligomerization (Figure 1), and by leading to brain microangiopathy [34]. For instance, the protein kinase GSK3, which

phosphorylates tau on several residues, is regulated by insulin through the PI3K-PKB pathway [35]. Besides hyperinsulinism, deprivation of insulin can also prove to be neurotoxic. Moreover, a deficiency in insulin may alter APP processing to favor b-amyloidogenesis via a combination of translational upregulation of BACE1 with elevations in its substrate, APP [36]. Insulin also promotes the release of intracellular Aβ and regulates expression of insulin-degrading enzyme, thus abnormally low brain insulin levels may result in increased intraneuronal accumulation of Aβ [37].

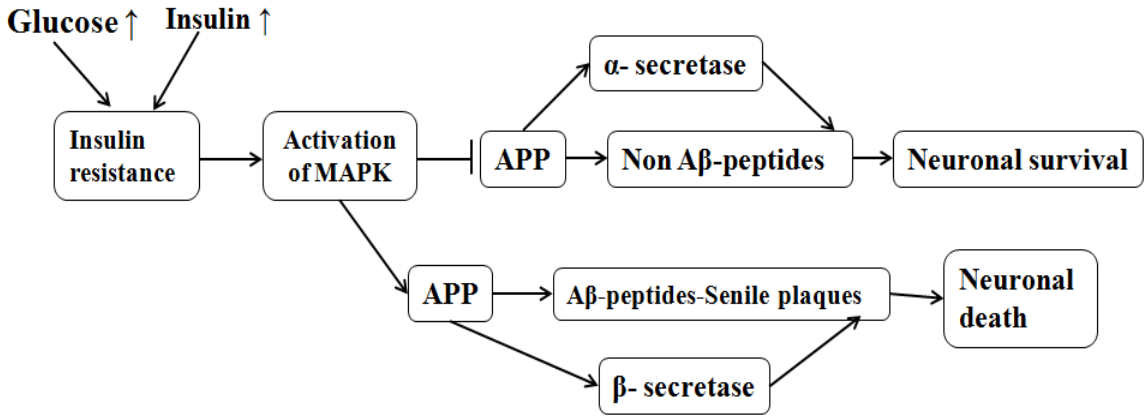

Figure 1: Schematic representation of the role of insulin signaling in the metabolism of β-amyloid and the impact of hyperglycemia and hyperinsulinemia in the activity of the amyloidogenic pathway. High insulin and glucose levels are proposed to promote the abnormal accumulation of toxic β-amyloid peptides.

Obesity

Obesity, a pathogenesis that can be defined as an excess of body fat, has reached epidemic proportions in our society. A host of adverse health outcomes are linked to obesity, including a higher risk of numerous medical conditions such as hypertension and DM [38]. While it is well established that each of these conditions are associated with adverse neurocognitive outcomes, there is also growing recognition for an independent effect of obesity on brain function (see Table 3). Accumulating evidence based on clinical and epidemiological studies support the suggestion that midlife obesity represents a major risk factor for various types of dementia, such as AD. A meta-analytic review of 15 prospective studies (follow-up ranged between 3.2 and 36.0 years) [39] revealed that relative to normal weight BMI categorization, an overweight BMI in midlife imposed a 1.35 times greater risk for presenting AD. Obesity has also been linked with neuropathological changes often considered to be distinctive of AD. There are many possible factors and mechanisms that may account for this relationship. In fact, several studies suggest that adipokines, and in particular leptin, may influence the pathogenesis of AD [40]. Lieb et al. [41] reported that higher levels of leptin were associated with a higher incidence of dementia including AD. Additionally, relative to non-obese controls, severely obese persons exhibit higher levels of amyloid-beta precursor protein and tau expression in sections of the hippocampus [42]. This finding is consistent with data that demonstrate greater levels of plasma amyloid proteins in individuals suffering from obesity [43]. In addition, midlife overweight and obesity have been linked with blood brain barrier disruption [44], and widespread grey matter volume reductions. Systemic and central inflammation, as well as altered microglia and astrocyte expression, are among other factors involved in

neurodegenerative disease development negatively impacted by the presence of adiposity.

Table 3. *Summary of representative human studies on the relationships between obesity, AD, leptin and brain function*

Reference	Study Cohort	Observations
[45]	Kaiser Permanente Northern California Medical Group (longitudinal study, 27 years) 10,276 individuals; 713 developed dementia	Individuals who were obese or overweight (elevated BMI) at midlife are at increased risk for dementia.
[46]	Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study (random population-based longitudinal study, 21 years)	Midlife obesity (elevated BMI) is associated with risk of dementia and risk of AD.
[47]	Prospective Population Study of Women in Sweden (32-year-longitudinal study); 1,462 women, of which 161 developed dementia	Elevated midlife waist-to-hip ratio increases risk for dementia.
[41]	Framingham study (longitudinal study, 8.3 years); 5,209 individuals, of which 111 developed dementia and 89 developed AD	Higher leptin is associated with lower risk of dementia and AD
[48]	Cross-sectional study of 34 elderly individuals without dementia or metabolic syndrome	Higher leptin is associated with increased gray matter volume in the hippocampus and cerebellum.

Conclusions and future perspectives

The present review reinforces the view that DM and obesity are strongly associated with multiple deviations from the proper functioning of the brain, by focusing on possible links between these disorders and AD. Evidence indicates an association among peripheral hyperinsulinaemia, insulin resistance, glucose dysregulation and increased risk of AD. Several studies have also reported that insulin regulates amyloid concentrations, with increased and decreased insulin concentrations being proposed to promote AD pathogenesis through differing effects on Aβ release and clearance. Whether insulin dysregulation merely superimposes the general consequences of disrupted energy metabolism, oxidative stress, inflammation, and reduced neuroregeneration on a pre-existing disease-specific neurobiological template, or whether distinctive abnormalities related with insulin metabolism occur that make unique contributions to AD, is unknown and remains to be elucidated. In terms of BMI and leptin, obesity and increased peripheral leptin have been associated with the incidence of AD. Obesity has been found to increase the risk for AD though abnormalities in peripheral metabolic factors, but the mechanisms that account for these phenomena are not entirely known. In the past few years it has became increasingly clear that adipocyte dysfunction influences the risk and/or the rate of cognitive decline, with several adipocytokines exerting differential

protective or deleterious effects on cognitive-related structures. Recently, the effects of adipokines, in particular inflammatory adipokines, have received attention with regards to AD and further examination of their contribution is warranted. Regardless of the specific cause, the establishment of a close relationship between the diabetes mellitus, obesity and Alzheimer's disease could open a large vein for the development of novel preventive and therapeutic interventions.

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The allostatic load caused by surgery

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Abstract

The allostatic load is described as a combination of somatic and neuropsychiatric damage which is carried along one's health status as a permanent and irreversible result but is also closely related to socioeconomic factors. The allostatic load caused by surgery has very much to do with surgical stress which varies according to the kind of operation and existing comorbidities. Anesthesia, analgesia, long stay in Intensive Care Units, and post - surgical interventions consist what the surgeon himself may cause as an independent prognostic factor. Any surgical operation may cause a sequence of physiological responses which in major surgery may take place out of the homeostatic range. When it does, an allostatic process determines the ultimate route to survival. When a major operation takes place, with long duration and severe violation of the involved organs physiology, then brain, liver and adrenals react with scientifically documented patterns described by the theories of the organ axes. According to its first literature appearance, allostasis has been described mostly as a cumulative damage and not as a sudden shock, so it is accepted that surgical operations might play a crucial role in allostatic chronic conditions or major postoperative disabilities. Surgical diseases that could represent allostatic phenomena are Inflammatory Bowel Diseases (IBD), morbid obesity before and after a bariatric operation, post-injury conditions (multi-trauma cases), patients before and after transplantation, and patients with stomas or long-standing artificial enteral nutrition. Old age and concomitant diseases are significant factors for developing fast allostatic changes which can be documented with stress -related biochemical testing. Common preoperative tests are planned under the limitations on low-cost health services. Thus, patients that undergo major operations are in greater risk of allostatic changes, due to the combination of aging, concomitant diseases and hidden predisposing factors (unrevealed with common tests). In dementia, preoperative preparation is a very sensitive and less studied issue, even for patients who have already been diagnosed for dementia and have received personalized therapies and been followed up for years.The special role of the pre-anesthetic examinations could be more extensive in Bariatric Surgery and in Inflammatory Bowel Diseases.

Keywords: Allostasis - Preoperative Diagnostic Tests – Dementia

Introduction

Allostasis is a theoretical term which has expanded through the years, it was introduced by McEwen [1] in 1998, it still exists in medical bibliography wider than ever in meaning, exactly because it is modern, responds to real data of social and clinical sciences, and connects society, health and genetical alterations. McEwen introduced allostasis to explain bad health resulting in populations lacking socio-economic prosperity. The allostatic load was used as a variable which never declined because, according to the theory of allostasis, this kind of "dyshomeostasis" could only worsen and

was incurable.

Allostasis is not used as a synonym of the term dyshomeostasis. Selye [2], in 1946, described that lack of hormonal balance may lead to failure of adaptation in environmental changes. Since then, many scientists referred to dyshomeostasis as a failure to adaptation. On the contrary, allostasis refers to success of survival thanks to changes which can be described by the allostatic load.

Socioeconomic status (SES) is an almost unchanged risk factor and bad prognostic criterion for any kind of disease arising in conditions of chronic stress. This had been the background for the birth of the term allostasis [1], which in turn was described again and again, altered in a sophisticated way- but not inaccurate - as it extends from the society and recently is linked to cell functions as well as the DNA of humans and mammals. The connection of social disparities and health were first done with the introduction of the term allostasis.

The biochemical description of allostasis was succeeded thanks to the laboratory findings about the family of kynurenines [3]. Allostasis, dyshomeostasis, fatigue and kynurenines are perfectly combined according to new theoretical models of disease [3]. Kynurenines are metabolites of L-tryptophan, and are produced via the kynurenine pathway. This pathway is controlled by the immune system and it is altered in neurodegenerative and other neurological diseases, in depression and in schizophrenia. Kynurenines might be defined as the biochemical imprint of the allostatic load. Kynurenines are present in any stress condition and play a predicting role in hereditary diseases, like schizophrenia [4]. Chronic stress is also related to the family of kynurenines, and their changes in connection to the autonomous nervous system, the immune system, the stress induced neurotoxic effects to the brain and the development of depression [5]. If kynurenines may describe the hereditary allostatic load this remains a challenge for the future.

While allostasis has been described with clinical and not sociological scope, its appeal among clinical doctors remained vague for some years. This happened due to the huge gap between theory and clinical practice. Also, clinical medicine never refers to poor and rich people, and predisposing conditions in medical history do not include socioeconomic status. However, when clinicians decided to use allostasis in their papers and utilize at last this valuable term, brain imaging contributed in the apprehension of the allostatic load irreversibility [6] but the real revolution took place when modern biochemical markers of stress were linked to genes, and thus the term “inherited allostatic load” [7] covered the missing theoretical part for the non- sociological aspect of allostasis.

Aim of the study-Methods

With the purpose to examine if surgical diseases are included in the group of allostasis related conditions, respecting the definition of 1998 by McEwen and the rest of scientific work related to this theory, the present article recalls known facts of surgery and determines the allostatic load caused by surgery. A number of 19 articles were chosen for review, with the use of the term words allostasis, surgery, preoperative diagnostic tests, dementia, and aging.

Results

The term allostasis is related to 653 articles in Pubmed database. Under the limitation “allostasis and surgery” a sub-group of 20 related articles were found. Among them, only one article refers to the possibility of having better surgical results if we respect the theory of allostasis in planning anesthesia and analgesia. Interestingly, there is not any article describing the use of allostatic load as a consequence of any operational technique.

Surgery has not been connected to allostasis, except one article only, coming from Dr. Chong V at al. [8], who combined the term socioeconomic status and the term operative risk, and for this reason, health outcomes were studied in correlation with education, income, and occupation. In clinical practice, the SES of patients is never reported in the personal history and does not play a role in Apache Score, which represents an algorithm commonly used by anesthesiologists to describe the physical condition [9]. On the other hand, chronic stress has been closely related to surgical diseases, as inflammatory bowel syndromes, morbid obesity, multiple trauma, transplantation procedures and surgical artificial openings (defecation stomas and feeding stomas).

Coleman LS [10], in his article titled “30 years lost in anesthesia theory” suggests that allostasis is a component of operative stress and limits its power in cognitive function. Coleman makes the conclusion that anesthesia, analgesia and allostasis are three factors that may lead to a good or bad surgical outcome. He uses the theory of “Stress Repair Mechanism” for describing three synergistic pathways: the spinal pathway, the cognitive pathway and the tissue pathway. Allostasis is connected to the cognitive pathway, which is modulated by emotional mechanisms. Anesthesia inhibits the cognitive pathway. Analgesia inhibits the spinal pathway. The synergistic combination of anesthesia and analgesia are prohibiting the hyperactivity of the Stress Repair Mechanism [10]. Recently, a Greek prospective study has confirmed the prolonged impact of anesthesia on cognitive function [11], and the relation of emotional disorders and allostasis is also reported in scientific publications [3].

Traumatic early and late neuroendocrine response [12] might be categorized in allostatic changes related to surgery. Since survival or death is the final status of the teleological route for allostatic mechanisms, neuroendocrine defects and dysfunctions, can be studied as post trauma allostatic phenomena, early and late. We never refer to early allostatic changes and late allostatic changes, because allostasis is described as a cumulative and irreversible damage, which worsens only [1].

Allostasis has not been studied as a clear neuroendocrine phenomenon, but is crucially bonded to neuroendocrine hormones. Aging is related with allostasis due to the accumulative character of physiological damages as well as the hormonal degradation related to aging. In clinical death, hormonal therapy is administered to maintain organ vitality until the consent of the family is received [13].

Cancer is also connected with aging. Cancer has not been connected to allostasis, but has been related to kynurenine, which is the *fingerprint of allostasis* [14]! Hormonal therapy is an option for some types of cancer. It would be interesting if hormonal therapy could be given to reduce the allostatic load that is carried along cancer physical history. We already know that glutamine administration reduces the production of kynurenine [15] and probably the suitable hormones will be proved to be neuroendocrine hormones or neurotransmitters. Recently this knowledge has been expanded because 19 amino acids were found to help towards reductions of kynurenine levels, in experimental studies [16].

The positive action of 5-hydroxytryptamine (5-HTP) in inflammatory bowel diseases (IBD) is

documented [17]. Allostasis of IBD is clear [18]. If the anti-depressive therapy could help in allostatic load it is not found, as according to the definition of allostasis the damage is irreversible, and gene faults in several allostatic conditions [4] support the definition of 1998. However, according to Dr. Nathalie Castanon [19], inflammation and mood disorders are linked via the activation of the kynurenine pathway, and in the same work the researcher expands her results to obesity and related comorbidity, too.

The difficulty to recover after an admission in ICU is greater in old people. Early worsening heart failure has been reported when anesthetic drugs are stopped. If neuropsychiatric medication replaced a part of the custom sedation protocol administrated to ICU patients, then stress might be alleviated and awakening might be facilitated without the morbidity and mortality reported so far. Neuroleptics, like sulpiride, have been recognized as helpful drugs for patients with response to inhibit kynurenine metabolism [20]. Administration of adrenaline helps in the arterial pressure abnormalities but does not help with stress and related allostatic damage in ICU. Adrenaline raises stress and provokes a “neuroendocrine storm”. On the other hand, in “rescue therapies”, hydrocortisone offers a hormonal lifting to the patients but may cause predisposition to infections.

Discussion

Allostasis has never been correlated with the kind of surgery used in critically ill patients. Surgeons may contribute to the reduction of operative stress by using new technologies in the field. For example, minimal invasive surgery is a very important novelty because it lessens pain and succeeds in full recovery and return to work much faster than classic procedures. Robotic surgery is appraised for less loss of blood and geometrical accuracy in surgical dissection leading to less tissue damage. The total operative stress is not yet determined in minimally invasive surgery and robotic surgery, with the use of biochemical biomarkers. It is generally accepted that modern surgical procedures are welcome if their duration is equal or shorter than the open technique.

Operative stress and Allostasis

The result of the operative stress after one or more surgical interventions may be calculated in the long term if a serious complication changes permanently the quality of life and allostatic changes are established. For example, if a disability occurs early after an operation, the allostatic load that is produced is not yet possible to be calculated, because the recovery period includes all the changes needed for gradual improvement. After a considerable time needed for re-evaluation, the conditions that we decide to determine as “irreversible” combine the allostatic load caused by surgery. The time needed to announce permanent physiologic damages to our patient vary according with the operation conducted.

Timing for Operation

The pre-operative preparation of the patient is very important for the success of the operation and the avoidance of complications. For example, major and urgent operations have tremendously higher mortality and morbidity [21]. For aged patients, the numbers are worse [22]. Because we cannot always avoid the operation in elderly, kynurenine levels might help us to prepare the patient for a major operation with all available means. Even the patients themselves might be more skeptical for the decision to sign a consent form, if they knew the real danger of a possibly unneeded or very dangerous operation.

Choice of the Operational Technique

All patients are not suitable for every operational technique. Geriatric surgery has been developed via modern surgical equipment. Minimally invasive surgery is the best way to reduce postoperative morbidity and mortality. In my opinion, patients with a higher allostatic load should be treated differently. For example, patients with morbid obesity and patients with inflammatory bowel diseases are the two first groups of patients that should be tested for their kynurenine levels pre-operatively. Kynurenine levels may become a new pre-operative criterion for anesthesiologists and surgeons as well as intensivists. Many times, ICU provides a temporary safety to patients that die as soon as they leave the mechanical support (or relatively soon).

Allostasis maintains life in patients with severe but not lethal complications. This “physical resistance to death” could resemble with the numerous changes of resistant bacteria in complicated and prolonged infectious diseases. It is already reported that immunological response has a correlation with allostasis [3]. When allostasis is already present before the operation, the expected prognosis is definitely different. A correlation of kynurenine and immune-mediated inflammation has been reported [23]. Trauma physiological mechanisms, have also been related with special immunological changes. We already know that kynurenine pathway is strictly controlled by immune mechanisms, thus the immune and neuroendocrine response in postoperative stress may be successfully calculated before a major operation is conducted [5].

Conclusions

A wise pre-operative preparation is one of the best ways to avoid an increase in morbidity and mortality in patients with recognized allostatic load - or not recognized! The introduction of new pre-operative markers, as kynurenine family tests, as well as the use of novel pharmaceutical stress-relieving drugs (especially those targeting to the kynurenine pathway) is a future prospect for improving surgery results for aged patients, the safe conduction of oncological therapies, and the facilitation of treatments in chronic inflammatory gastrointestinal diseases as well as in morbid obesity.

The author declares that has no conflicts of interest

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Encapsulation of flavonoid quercetin in PEGylated SiO_2 nanoparticles against Cu(II)-induced oxidative stress.

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Abstract

Alzheimer's disease (AD) is a neurodegenerative complex process associated with progressive brain damage and cellular demise. An important factor that significantly induces the development of oxidative stress and neuronal cell death is the presence of biochemically redox active metals as Cu(II). Poised to develop antioxidant molecular nanotechnology, we synthesized hybrid PEGylated SiO_2 nanoparticles (NPs) as host-carriers of the natural flavonoid quercetin (QC). The synthetic NPs were physicochemically characterized with particle size, z-potential, FT-IR, TGA, BET and SEM. Determination of the entrapment efficiency and drug release studies were performed through UV-Visible spectroscopy. The biological profile of quercetin-loaded nanoparticles in a cellular Cu(II)-induced neurodegenerative environment indicated the improved specificity of the novel nanoparticles against oxidative stress, signifying the development of molecular protection and preventive medicinal nanotechnology against AD.

Keywords: Quercetin – Neurodegeneration – Encapsulation - SiO_2 - Copper

Introduction

Alzheimer disease (AD) constitutes the most common form of dementia [1]. It causes a progressive deterioration of cognitive function to aged people (>65 years old), causing severe brain damage [2].

Oxidative stress is the result of an imbalance in the reactive oxygen species (ROS) production and antioxidant defensive mechanisms [3]. In this regard, experimental evidence indicates that ROS may participate in the pathogenesis of neurodegenerative diseases such as AD, and a part of these diseases seem to be mediated by oxidative stress mechanisms and accelerated by focal ageing [4].

Oxidants are generated as a consequence of normal intracellular metabolic procedures in mitochondria and peroxisomes and from various cytosolic enzyme systems. Furthermore, ROS production can also be triggered by a number of external agents. ROS levels can be counteracted and regulated by enzymatic and non-enzymatic antioxidant systems such as catalase, superoxide

dismutase and glutathione peroxidise in order to maintain physiological homeostasis. Decrease of ROS levels below the homeostatic set point interrupts the role of oxidants in host defence and cellular proliferation. In a similar way, the increase of ROS caused by damage to proteins, lipids and DNA, may lead to cell death or to the acceleration in ageing and age-related diseases, activating redox-sensitive signalling pathways [4].

Much of the research in AD has demonstrated evidence on the importance of oxidative stress mechanisms in its pathogenesis. Cellular alterations indicate oxidative stress and free radical damage as the main etiologies of the hallmark pathologies in AD. Moreover, during the spatio-temporal distribution of this damage, all neurons vulnerable to death in the disease are involved. Oxygen radicals induce lipid peroxidation [5,6], and advanced glycation end products [7], nitration [8], carbonyl-modified neurofilament proteins or free carbonyls [9,10] causing cytoskeletal abnormalities and senile plaques alterations.

Current research evidence point out that the source of the shift in oxidative homeostasis is the consequence of the changes in the balance of redox active metals like copper (Cu), that undergo redox cycling reactions producing reactive radicals in biological systems and. Accumulation of copper is a major source of the ROS production, which are responsible for the oxidative stress parameters in AD as copper is present at significantly high levels in AD neuropil and lesions. Detection of Cu redox activity can be enhanced by adequate chelators of biological importance [11].

Several studies evaluate the effects of anti-inflammatory and antioxidant compounds on AD, such as naturally occurring antioxidant flavonoids [12]. Flavonoid quercetin (QC) is a natural polyphenolic compound [13], with effective anti-carcinogenic [14], anti-oxidant [15], and anti-inflammatory properties [7]. QC has been proved to be effective against oxidative processes and cytotoxicity, improving memory function and learning ability [16]. Nevertheless, poor absorption and difficulty in traversing the Blood-Brain-Barrier (BBB) prevent its action in the central nervous system [17].

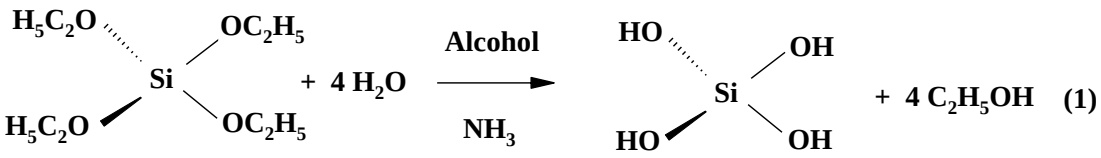
Sol-gel derived silica xerogels constitute an important class of biodegradable materials for drug delivery operations finding applications as biocompatible coatings on implants [18], biocatalysts [19], biosensors [20], and carriers for controlled release of vitamins, [21], pharmaceuticals, and biocides [22]. The main advantage of sol-gel materials is their ability to encapsulate various natural or synthetic therapeutic substances for controlled drug delivery applications [23]. Silica xerogels possess unique properties, such as stable porous structures, tunable pore sizes and volumes, large surface areas, and well-defined surface properties for site specific drug delivery and hosting of molecules with various shapes, sizes, and functionalities [24], with enhanced permeability, retention effect, long blood circulation half-lives, and sustained release rates [25]. In pursuit of such technology, PEGylation of NPs has been studied [26].

Poised to encapsulate water-insoluble drugs into silica xerogels, targeting novel, antioxidant nanotechnology, we have a) synthesized base-catalyzed silica NPs modified with PEG 3000, b) evaluated the suitability of these matrices as nanocarriers for the controlled release of the flavonoid quercetin, and c) investigated the cytotoxicity and potential protective effects under Cu(II)-induced oxidative stress in *in vitro* primary hippocampal cultures. The new nanomaterials are expected to contribute to: i) improved therapeutic activity, ii) protection against QC degradation, iii) pharmacokinetic optimization and control of QC biodistribution, and v) decreased cytotoxicity as a result of an efficient QC release rate, counteracting Cu(II)-induced oxidative stress.

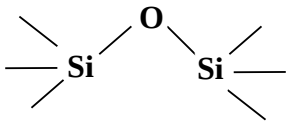
Methods

Synthesis

SiO_2 xerogels were prepared by hydrolysis and polycondensation of TEOS as described in Eq. 1 [10,27], followed by aging and drying.



Condensation of the emerging hydrated SiO_2 tetrahedra gives rise to moieties such as those shown below:

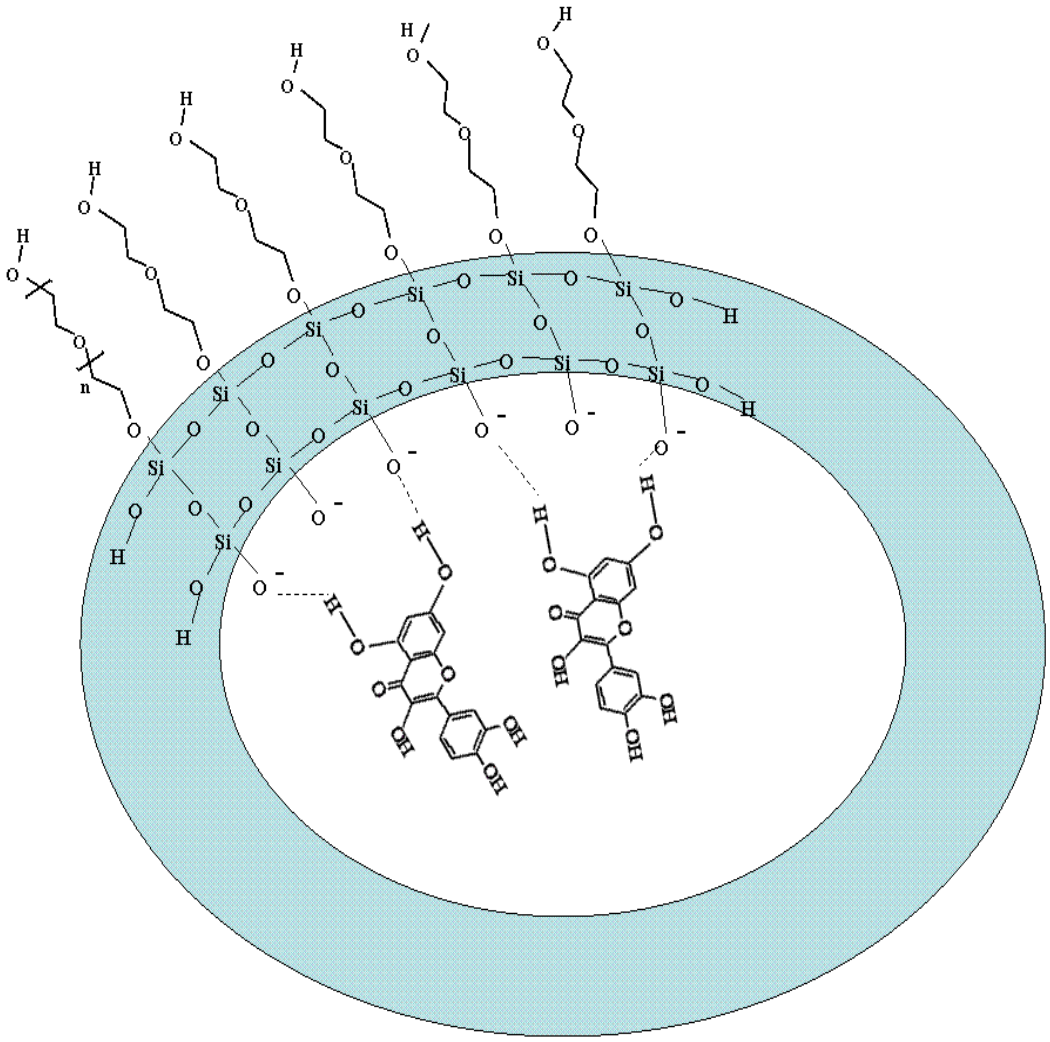


The products of the overall synthetic process are alcohol and water. Following formation of SiO_2 spheres, PEG 3000 was added to silica sols, in order to modify SiO_2 matrices. The reaction describing the PEGylation of SiO_2 NPs is shown in Eq. 2 [28]:

$$2Si(OH)_4 + HO\text{-}CH_2\text{-}CH_2\text{-}(O\text{-}CH_2\text{-}CH_2)_n\text{-}OH \xrightarrow[H_2O\text{-}EtOH]{NH_3}$$

$$(HO)_3\text{-}Si\text{-}O\text{-}CH_2\text{-}CH_2\text{-}(O\text{-}CH_2\text{-}CH_2)_n\text{-}O\text{-}Si(OH)_3 + 2H_2O \quad (2)$$

To the modified SiO_2 sols increasing amounts of QC (0.25, 0.50, 0.75 g) were added. A representative model of QC-loaded PEGylated SiO_2 NP is shown in Scheme 1:



Scheme 1: Schematic illustration of the QC@PEG-SiO_2 NP.

Physicochemical characterization

For the physicochemical characterization of the synthesized materials different complementary techniques such as particle size, z-potential, FT-IR, TGA, BET and SEM were applied. The entrapment efficiency and the *in vitro* QC release study were determined through UV-Visible spectroscopy at the characteristic wavelength of QC absorption (370 nm) [29].

Cell survival assessment upon QC vs. Cu(II) exposure

Sprague Dawley rat neonates (1-3 days old) were used to prepare hippocampal cultures after cervical dislocation in accordance with the Department of Veterinary Medicine of Aristotle University regulations.

All animal care and treatment followed the European Community Council Directive of 24

November 1986 (86/609/EEC) and the guidelines for animal experimentations of Aristotle's University Research Committee.

All procedures contributing to this work comply with the ethical standards of the laws of Greece according to the Hellenic National Bioethics Commission on the care and use of laboratory animals. Detailed cell culture experimental procedure is described in our previous work [30,31]. Upon piloting, concentrations and incubation period of interest used for QC and CuGly were determined. Cell viability was assessed, cultures were stained using live/dead Cell Double Staining Kit with further modification of the protocol (Sigma Aldrich, UK). Images were visualized using an Axioskop 2 plus microscope (Carl Zeiss, Germany) with a 40x phase contrast water immersion objective. They were captured using an AxioCam HRc camera, controlled by AxioVision software (Version 3.1) using the appropriate Rhodamine (for propidium iodide -PI) and Fluorescein isothiocyanate (FITC; for calcein) filters. ImageJ software (version IJ 1.46r) was applied for manual cell counting assessment. Each experiment was conducted in triplicate and repeated at least three times, thereby ensuring that a suitable number of replicates (n = 9) were sampled for each treatment for statistical analysis. Statistics were calculated using GraphPad Prism1 (Version 4.01; GraphPad Software, San Diego, CA, USA). Mean viability rates and SEMs were calculated for each group and cell type. One-way statistical analysis of variance (ANOVA), followed by Tukey's multiple test comparison test, was performed considering all group pair comparison. Degrees of significance were assessed by three different rating values: *$p<0.05$ (significant), **$p<0.01$ (highly significant) and ***$p<0.001$ (extremely significant) or non-significant ($p>0.05$).

Results

The QC-loaded SiO_2 NPs provided a well-defined, highly stable system in its handling in physiological media and projected a variable loading capacity of the flavonoid with a concurrent and almost complete release of its load during drug release experiments.

BET measurements indicate that the average pore size of the emerging NPs decreases with rising amounts of QC. However, the surface area and pore volume increase with increasing amounts of QC. In addition, pore size distribution becomes narrow with increasing amounts of QC.

According to SEM all PEGylated xerogels have an illegible interface, smooth and compact wall surfaces and consist of discrete, lamellar porous particles and cracks on the shell surface.

Particle size measurements showed that the novel NPs were of submicron size and of low polydispersity with a relatively narrow particle size distribution. Zeta-potential measurements showed a negative surface charge due to the surface PEG alcoholic groups. As QC load increases, a significant increase is also observed in surface negative charge.

The in situ loading efficiency of QC@PEG-SiO_2 samples (0.25, 0.50, 0.75 g) was estimated to be 58.2%, 78.4% and 89.6% (±5%), respectively. The equilibrium cumulative QC release percentages from QC@PEG-SiO_2 samples (0.25, 0.50, 0.75 g) were estimated to be 69.9%, 87.7%, and 98.2%, respectively.

Entrapment and release studies revealed the dose dependence behaviour of the loading capacity

of the NPs in QC and the complete release of that load under Cu(II)-induced oxidative stress conditions in neuronal and glial cultures by soluble Cu(II) (Copper glycinate-CuGly).

As shown in Figure 1, neuronal cell viability was 91±1%, 86±1% and 62±1% ($p<0.001$) in the presence of QC-PEG NPs at QC concentrations of 30 μM, 150 μM and 300 μM, respectively, compared to untreated healthy neurons. The combination of QC-PEG NPs at 30, 150, 300 μM and 10, 50, 100 μM of CuGly, respectively, showed 96±2% ($p>0.05$), 94±2% ($p<0.05$) and 44±1% ($p<0.001$) neuronal cell viability compared to the control. Treatment of neuronal cells with CuGly at 10, 50 and 100 μM afforded 85±1%, 78±1%, 55±2% ($p<0.001$), respectively, cell viability compared to the control. Further comparison of the QC-PEG/CuGly combinations to the individual QC-PEG and CuGly treatments was also carried out. No differences on viability rates were indicated upon comparison of [QC-PEG 30 μM + CuGly 10 μM] and 30μM QC-PEG ($p>0.05$), whereas [QC-PEG 30 μM + CuGly 10 μM] was statistically different from CuGly 10 μM ($p<0.001$). Further observations were made for the remainder of the combinations. Specifically, [QC-PEG 150 μM + CuGly 50 μM] was significantly different from 150 μM QC-PEG ($p<0.01$) as well as from CuGly 50 μM ($p<0.001$). The above results indicate that lower concentrations of QC-PEG were protective for neurons against the lower concentrations of CuGly. In contrast to that, [QC-PEG 300 μM + CuGly 100 μM] was different from 300 μM QC-PEG ($p<0.001$) and CuGly 100 μM ($p<0.001$), implying that the highest concentration of QC-PEG could not protect the neuronal cells against the highest concentration of CuGly as it itself was toxic to the cells.

Moreover, the glial cell population stood at 97±2% ($p>0.05$), 95±2% ($p>0.05$) and 87±2% ($p<0.01$) at concentrations 30 μM, 150 μM and 300 μM of QC-PEG NPs compared to the untreated glial cells. Moreover, glial cell viability in the presence of [QC-PEG 30 μM + CuGly 10 μM], [QC-PEG 150 μM + CuGly 50 μM] and [QC-PEG 300 μM + CuGly 100 μM] was recorded at 91±2% ($p<0.05$), 90±2% ($p<0.01$) and 81±2% ($p<0.001$), respectively, compared to the untreated cells. Finally, glial cell treatment with CuGly at 10, 50, 100 μM led to viability rates at 89±2% ($p<0.01$), 87±2% ($p<0.001$), and 78±1% ($p<0.001$), respectively, compared to the untreated glial cells. Additional analysis of the QC-PEG/CuGly combinations to the individual QC-PEG and CuGly treatments indicated no differences among [QC-PEG 30 μM + CuGly 10 μM], 30μM QC-PEG ($p>0.05$) and CuGly 10 μM ($p>0.05$). Similar observations were made for the rest of the combinations in glia. Specifically, the presence of [QC-PEG 150 μM + CuGly 50 μM] in glial cells was found not significantly different from 150 μM QC-PEG and CuGly 50 μM ($p>0.05$).

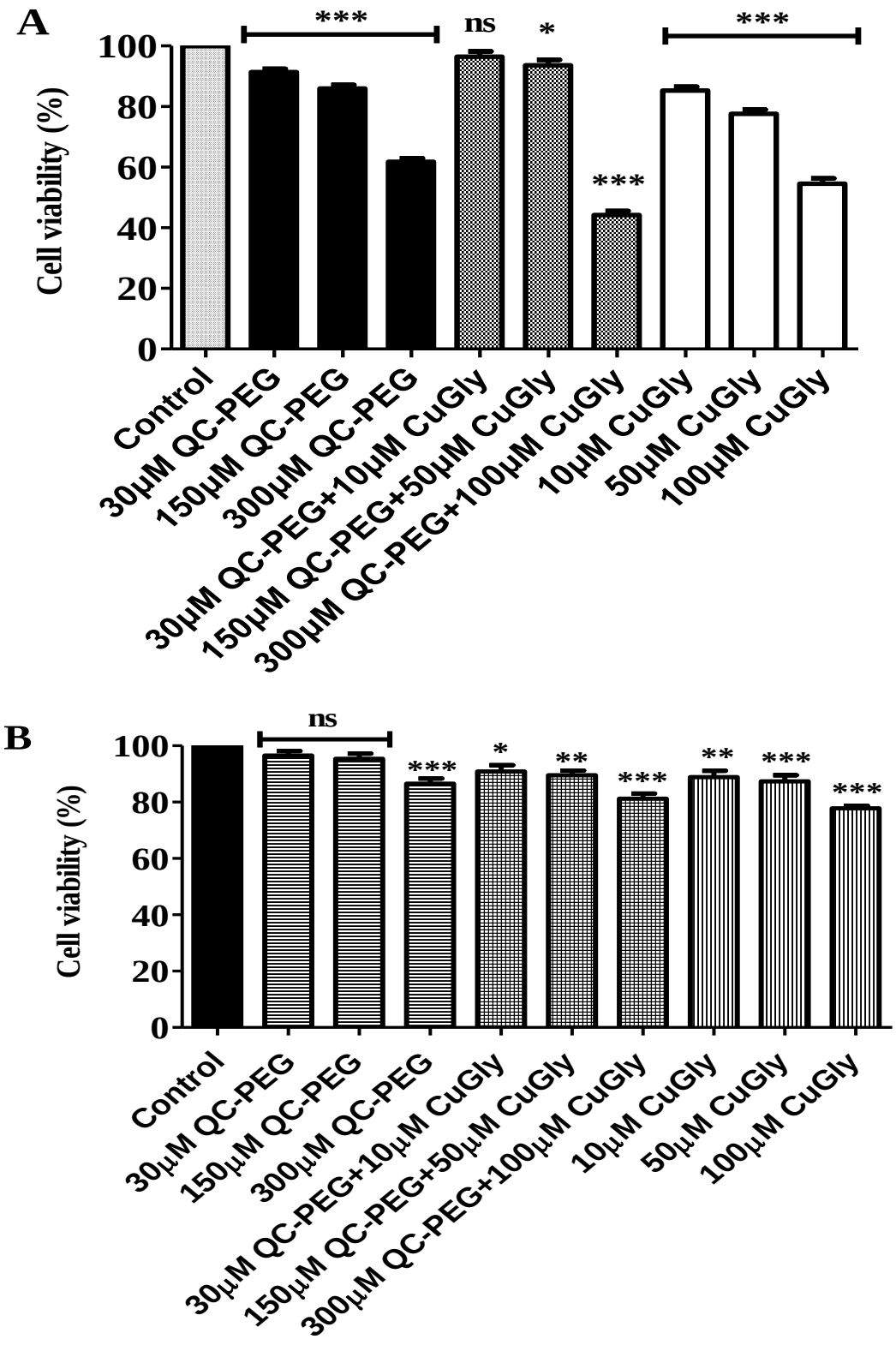


Figure 1. The action of QC-PEG (30-300 μM) in combination with CuGly (10-100 μM) was assessed on the viability rate of rat primary hippocampal neurons (**A**) and glia (**B**). Individual experimental conditions of QC-PEG (30-300 μM) or CuGly (10-100 μM) were also run. 24 and 3h incubation period was employed for QC-PEG and CuGly, respectively. Data are shown as means, relative to control (untreated) viability rates recorded in the absence of QC-PEG and CuGly (in % +SEM). Statistical differences are indicated as $p>0.05$ (ns = non-significant), $p<0.05$=* (significant), $p<0.01$=** (highly

significant) and p<0.001=*** (extremely significant).

Additionally, [QC-PEG 300 μM + CuGly 100 μM] was not different from 300 μM QC-PEG and CuGly 100 μM (p>0.05). However, the presence of QC-PEG (30 or 150 μM) could improve glial cell viability against CuGly, at lower concentrations (10 or 50 μM). The highest concentrations of either QC-PEG (300 μM), CuGly (100 μM), and their combination, affect glial cell viability at the individual and combined level (p<0.001).

The collective *in vitro* results demonstrate that encapsulation of QC at physiological pH enhances its solubility and bioavailability to cellular media and the cells themselves and protects QC from degradation. The collective results set the stage for the development of medical nanomaterials against Cu(II)-induced oxidative stress in neurodegenerative diseases.

Discussion

QC encapsulation in inorganic hybrid hosts against neurodegeneration.

Various types of molecular nanocarriers have been used for the encapsulation of active biomolecules that enhance physiological metabolic processes counteracting pathogenetic phenotypes for the remediation of cellular diseases, such as dementia and its progressively worsening condition, AD. An important factor to confronting molecular events in intracellular neurodegenerative processes is access to cellular targets beyond the BBB and into neuronal networks affected by the disease.

In view of the fact that oxidative stress constitutes a major factor in the induction of cellular degeneration in AD, providing countermeasures as a defensive approach stands as a logical and plausible strategy in order to provide solutions against deterioration of the disease. In view of the existing limitations toward access to biological sites of interest and targeted delivery of bioactive antioxidant compounds, a formidable research challenge is the development of nanocarriers with the ability to bypass accession restrictions, toxicity, biochemical reactivity and biocompatibility.

Cognizant of the known imbalance between pro-oxidants (e.g. metal ions) and anti-oxidants in oxidative stress, the choice of potent naturally occurring antioxidant flavonoids is a logical alternative. Flavonoid QC was employed in this research to be encapsulated in an appropriate hybrid inorganic matrix, such as SiO_2. The structural characteristics of QC, such as its peripherally located ketonic and phenolic moieties and the bulky aromatic trunk, along with its metal chelating ability and electron delocalization potential, present an active antioxidant biomolecule with uniquely configured hydrophobic-hydrophilic behaviour, capable of interjecting ROS-RNS species, contributing to the neutralization of the Fenton and Fenton-Weiss reactivity, during oxidative stress processes in a neuronal environment.

In an attempt to develop efficient drug nanocarriers for the QC encapsulation and targeted delivery, the stable and low toxicity inorganic matrices of PEGylated SiO_2 NPs were used as hosts. PEGylation has been extensively used as an effective approach to develop stealth nanomaterials in order to reduce the non-specific binding of NPs to blood proteins and macrophages, and the agglomeration degree through steric stabilization, thereby increasing stability during storage and application [32].

The encapsulated QC in sol-gel derived PEGylated SiO_2 xerogels provided a well-defined, appropriately surface-modified hybrid system, with enhanced stability in its handling in physiological media and low toxicity compared to other liposomal and polymeric nanocarriers. The hybrid nanocarrier projected a variable loading capacity of QC with a concurrent and almost complete release of its load during drug release experiments.

Chemical and biological profile of QC-loaded PEGylated SiO_2 NPs in neuronal cell cultures

Among the metal-chelating flavonoids, QC has been chosen in this study for its remarkable anti-oxidant properties [33], and its protective role against glutamate-induced oxidative toxicity and lipid peroxidation by blocking ROS production [25]. Furthermore, its hydrophobic behavior facilitates the pass into the cytoplasm, where ROS are generated, and modulate oxidative glutamate toxicity [25]. Moreover, due to its specific structure, QC prevents GSH oxidation [25], can penetrate into brain regions [34], pass through the BBB ensuring protection against H_2O_2-induced cytotoxicity [35]. Numerous research reports have focused on QC nanocarriers with low toxicity and enhanced mechanical stability [36-38].

Herein, for the first time, the present *in vitro* work employed QC-loaded PEGylated SiO_2 hybrid NPs against Cu(II)-mediated oxidative stress effects. QC-loaded NPs appeared effective against CuGly reactivity only at the lowest two concentrations of CuGly (10 and 50 μM) and only for the two lowest concentrations of the QC-loaded NPs (30 and 150 μM). The specific effectiveness was due to the QC release from the NPs and was more pronounced in the case of neurons.

At the highest concentration of QC-loaded NPs, neurons and glia behaved similarly, essentially suffering from toxic effects leading to their demise. Additionally, the hippocampal cells behaved similarly upon exposure to almost all concentrations of CuGly used to induce oxidative stress. The observed pronounced decrease of neuronal viability at high concentrations of Cu(II) and NPs might be due to: a) the different nature and reactivity of neurons versus glia and the inability of QC-loaded PEGylated NPs to counteract the high Cu(II) concentration-depended oxidative damage, and b) Cu(II) itself and QC, which at high concentrations appear to be toxic to the hippocampal cells (>200 μM) [39]. This is in agreement with our drug release study, showing that most of QC loaded in the modified SiO_2 NPs is released after an incubation period of >2h. Hence, a 24h incubation period was employed during the experiments to ensure consistently release of maximal QC concentration.

The results showed that particle-loaded QC tested, was less toxic to the hippocampal cell cultures, for the same concentrations reported in the literature; as in retinal pigment epithelial (RPE) cells [40]. In this regard, RPE cell viability stood at ~25%, upon a 24h incubation, for the highest QC concentration of 300 μM. In our experiments, glia were less affected, than neurons, by Cu(II) and QC, even at high concentrations. This observation is in agreement with literature, emphasizing the lower sensitivity of glial cells [41] and their protective role toward neurons [42].

Taking a further closer look at the results, key observations could be made on the behavior of the hybrid NPs in hippocampal cells under stress conditions. In that sense:

a) Free QC does not appear to be soluble and thus bioavailable. QC encapsulation enhances its solubility and bioavailability in the specific cells.

b) QC encapsulation at physiological pH protects it from degradation, which occurs rapidly in alkaline solutions [43]. The encapsulating and delivery procedures ensure the retention of the

physicochemical integrity of QC and its effective chemical reactivity at the site of release, respectively.

c) The selected QC, Cu(II) and NPs concentrations employed in this study are in line with physicochemical attributes such as the potential Cu(II): QC stoichiometries and coordination environment.

d) PEG3000 and PEG-modified NPs are not toxic to cells.

e) Potential accumulation of QC-loaded PEGylated SiO_2 NPs to be released inside the cells is also a possibility, yet one that would strongly depend on the metabolic activity of the cells under investigation [44]. To this end, future specific *in vivo* techniques [45] could contribute to probing, monitoring and understanding the processes of accumulation of the aforementioned NPs. Due to lack of suitable tracking methods, pharmacokinetic studies of SiO_2 NPs have not been reported extensively, as for other types of NPs, including SPIONs, TiO_2 NPs, and Au NPs [46-48].

Further investigation into molecular mechanistic aspects of the *in vivo* function of such hybrid material is therefore pursued in our laboratory, thereby targeting potential preventive and therapeutic interventions in neurodegeneration.

***Table 1**. Overview of all experimental compound groups and their concentrations.*

Compounds	Concentrations (μM)								
QC-agents (24 h)	_ 30	150	300	30	150	300	_	_	_
+									
CuGly (3 h)	_ 10	50	100	_	_	_	10	50	100

QC-agents= Quercetin in PEGylated NPs. CuGly= cis-[Cu(Gly)$_2$]H$_2$O.

Conclusions

PEGylated sol-gel SiO_2 xerogels were synthesized as nanocarriers of the flavonoid quercetin. The physicochemical characterization of the novel materials reflects the a) differential structural nature of the hybrid NPs, compared to other polymeric and liposomal drug nano-hosts, and b) significance and impact of PEG modification chemistry, projecting functional bio-reactivities upon exposure to neuronal cellular targets. The entrapment and release studies, reveal the competence of the NPs as far as the loading capacity and the release rate of their load under conditions of Cu(II)-induced oxidative stress in neuronal and glial cultures. The collective results set the stage for further work into the development of nanosized materials with preventive and/or therapeutic activity against metal-induced oxidative stress in neurodegenerative diseases.

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All authors declare that they have no conflicts of interest.

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From Kostas Ph. Grammatikos, A fish named clown anemonefish, aged about 1 year, in a private aquarium lying inside a tropical anemone which is aged 200-300 years. These anemones are poisonous to all fishes except the clown anemonefish. Beside are equipment supporting fish life in the aquarium.

A folk legend for the detection of dementia: an active part of online medical data entry channel

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Abstract

Objective: The early detection of cognitive disorders (CDs) is a main priority in the struggle against the exponential increase of the number of Patients with Dementia (PwD) globally. There are a variety of structured, validated, culturally sensitive, reliable and generally accepted screening tools. All of them are based on diagnostic criteria. However the majority of elders are not screened for a variety of reasons. The present work aims to develop and validate a culturally oriented screening tool, based on the legendary story of the Hagia Sophia cathedral (Church of the Holy Wisdom) at Constantinople (now Istanbul, Turkey). Method: This is an ongoing population-based study in an urban area of Greece (the Ilion Municipality of Attica). A total of 567 community dwellers (55+years old) participated voluntarily and were assessed on the Hagia Sophia Test (HAST), as well as the MMSE, the 3MS, and the CDT. The HAST was developed so that it can be administered by lay people. In the robust text of the myth, language deficits and/or impairment are detected in parallel with the cognitive functions. The test administration takes 10 minutes in total. Results: By estimating Pearson's product moment, statistically significant correlations were found between MMSE-HAST r=.447, 3MS-HAST r=.516, CDT-HAST r=.318, ($p<0.001$). ROC estimation of the screening value of the HAST with MMSE (cutoff 23/24) as a gold standard yielded 72.1% sensitivity, 72.1% specificity and 0.773 AUC.

Conclusion: This test, through its brief, friendly and ecologically valid nature, aims to support the increasing need for the screening of the elderly for cognitive disorders when appropriate.

Key words: Cognitive disorders - Culturally oriented screening tool - Greek population

Introduction

In 2015 it was estimated that 46.8 million patients suffered from dementia worldwide [Alzheimer's Disease International, 2015]. The number of patients will almost double every 20-year period and it is expected to reach 74.7 million by 2030 and 131.5 by 2050, while more ominous are the forecasts of the WHO [World Health Organization, 2015]. The fact that the estimate is 30% higher than the forecast of 2010 which was used in the 2012 WHO report [Alzheimer's Disease International, 2015] creates additional concern. The particularly high cost of dementia [Alzheimer's Disease International, 2015] in the near future is expected to exert high pressure to national health systems and the families bearing the care of PwD (see Table 1).

***Table 1**: The incidence of dementia worldwide [World Health Organization, 2015], its global, European [Alzheimer's Disease International, 2015] and national incidence [Tsolaki et al, 1999].*

	60-64	65-69	70-74	75-79	80-84	85-89	90+
Worldwide [WHO]	0,69	0,88	1,22	1,46	1,54	1,55	0,74
Worldwide [ADI]	1,0-3,3	1,7-4,4	2,9-6,0	5-8,6	8,0-15,2	13,1-27	23,5-57,5
Europe [ADI]	1,1-1,6	1,8-2,6	2,9-4,3	5-7,3	8,5-12,4	14-20,5	27,1-39,8
Greece [Tsolaki et al.]			4,84	6,82	5,88	6,25	33,33

Though it is clear that Alzheimer's Disease is associated with age, it is no tutterly associated with ageing [Ritchie & Fuhrer, 1992]. For Greece, the prevalence of dementia is estimated at 9.59 over 70 years of age [Tsolaki et al, 1999], while there is also a recent research on the prevalence of cognitive Disorders (CDs) in the population of Northern Greece [Tsolaki et al, 2014] and south Greece [Tsolaki et al., 2017).

The interaction of negative stereotypical views concerning ageing and, particularly, fears associated with ageing and the deterioration of physical health, memory loss, the potential burden on the family (especially on children) due to disability, and the threat of loneliness [Tsolaki et al, 2009], are culminated with the loss of people (partner, relatives or friends). The usually insidious onset of symptoms; the inability and/or reluctance to recognize and accept the existence and importance of early cognitive and behavioral changes [Ross et al, 1997]; the concurrent fear of diagnosis lead to the vicious identification-denial symptoms cycle, all delaying the seeking of help and diagnosis. The average two-year period interval from the first symptoms to the diagnosis of the disease [Larson, 2001], which for the Greek population ranges from 6 to 16 months for 52% of the cases [Tsolaki et al, 2009], creates significant problems in the daily life of the undiagnosed elderly: the benefits of pharmacological and non-pharmacological interventions, which are indicated for the early stages, are not exploited.

The information obtained by professionals (namely social workers, nurses, family carers) who communicate regularly with older adults is often not sufficient to identify major NCDs cases, as they usually lack specialized training. The elderly are normally unable to provide information and explanations for situations they experience difficulties with. They deny the existence of memory disturbances or other difficulties [Turvey et al, 2002]. There is a discrepancy between self-assessed memory disorders and selection test results in old people with major NCDs [Solias et al, 2015]. A recent study in England showed that 85% of the physicians and nurses working in community centres are able to detect major NCDs symptoms in the 58% and 84% of the cases, respectively [Moriatry, 2002]. The same author noted that clinical judgment alone is inferior to its combined use

with the administration of standardized selection tests, increasing thus the trace ability of major NCDs in the primary care.

The existing screening tests are easy to use, time-saving for the professional, and not tiring for the examinee. Moreover, they are generally neutral as far as the cultural traits of the population in question. They are based on diagnostic criteria, they meet strict standards of reliability and validity, with proven value over time in the detection of major NCDs, which continues to elude proper diagnosis.

This preliminary study aims to create a culturally oriented screening test for the detection of major NCDs, diverting from the culturally neutral ones. The target is twofold: a) to increase the percentage of elderly people who are roughly assessed for cognitive functioning and form part of a culturally homogeneous population; b) at a later stage, to attempt to create a combination model for culturally oriented corresponding tests for other populations.

Literature research did not reveal the existence of another relevant test which assesses mental disorders in the elderly in Greece or internationally.

The test:

The Hagia Sophia Test (HAST) draws on a popular legend that refers to the building of the Church of the Holy Wisdom at Constantinople (now Istanbul, Turkey) in the year 537 AD under the direction of the Byzantine Emperor Justinian I.

The combination of the natural and the supernatural elements often occurs in folk legends, providing a wealth of practical and useful information. According to one interpretation, the specific legend served as a sketch for the workers (about 10,000 mostly uneducated labourers), who needed to strictly follow the instructions of the architects who designed a 76.16 meters long, 71.82 meters wide and 54 meters high building. According to another interpretation of the legend, hexagonal, beehive-like stones needed to be used, adorning the building with excellent static features. This structure is found in the honeycombs which hold the extremely heavy (in relation to their thinness) load of honey and are not destroyed while being lifted and removed from the beehive. The supernatural element of Divine command (as in other similar legends) could yield much greater compliance with the requirements of project execution than any documented requirements on behalf of the engineers.

This text was originally used as a part of mental empowerment exercises. Older adults who did not cooperate or resented standardized tests were quite receptive towards a legend which forms part of their historical and cultural heritage. The Byzantine history is taught in our country and even those who have not formally learnt it are familiar with Justinian or Hagia Sophia, as it remains a benchmark of religious faith and folklore.

The text:

Όταν ὁ Αὐτοκράτορας	*When the Emperor Justinian*

Ἰουστινιανός στήν Κωνσταντινούπολη, ἀποφάσισε νά κτίσει τήν Ἁγιά Σοφιά, κανείς τεχνίτης δέν μπόρεσε νά τοῦ παρουσιάσει σχέδιο πού νά τοῦ ἀρέσει.	*decided to build the Hagia Sophia in Constantinople, no master could present him with a sketch he liked.*
Ὅταν μιά φορά πῆγε στήν ἐκκλησία νά λειτουργηθεῖ, ἐκεῖ πού ἔπαιρνε τό ἀντίδωρο ἀπό τό χέρι τοῦ Πατριάρχη ἔπεσε τό ἀντίδωρο κάτω. Σκύβει νά τό πάρει, δέν τό βρίσκει πουθενά. Ὅταν ξαφνικά βλέπει μιά μέλισσα μέ τό ἀντίδωρο στό στόμα νά πετᾶ ἔξω ἀπό τό παράθυρο.	*One day, he went to church to attend Mass. While he was taking the holy bread from the hand of the Patriarch, the holy bread fell down. He kneels to take it, he does not find it anywhere. Suddenly, he sees a bee with the holy bread in its mouth flying out the window.*
Βγάζει τότε διαταγή ὅποιος ἔχει μελίσσια νά τά τρυγήσει γιά νά βρεῖ τό ἀντίδωρο. Κανένας ἄλλος δέν τό βρῆκε παρά μόνον ὁ πρωτομάστορας, πού σέ μιά κυψέλη εἶδε ἀντί γιά κερήθρα, μιά πανώρια ἐκκλησιά πελεκητή καί πάνω στήν Ἁγία Τράπεζα τό ἀντίδωρο. Αὐτήν τήν ἐκκλησιά παρουσίασε ὁ πρωτομάστορας στόν Αὐτοκράτορα καί ἴδια μέ αὐτήν ἔκαναν τήν Ἁγιά Σοφιά.	*He then issues an order for all bee-keepers to harvest their beehives and find the holy bread. It was only the chief master who found it; he saw a magnificent carved church instead of a honeycomb in a beehive, and on top of the Holy Altar there stood the holy bread. This was the church which the chief master presented to the Emperor and Hagia Sophia was made just like it.*

Method of administration:

It takes 1':30" to read the text. The examinee is asked to focus on the reading task without trying to memorize the content. After reading the text, they are asked to perform another activity which attracts their attention (5'). Then, they are invited to fill in the blanks (maximum time: 4') in a semantically acceptable way.

The text given for completion:

Ὅταν ὁ Αὐτοκράτορας Ἰουστινιανός στήν ……, ἀποφάσισε νά κτίσει τήν …… ……, κανείς τεχνίτης δέν …… νά τοῦ παρουσιάσει σχέδιο πού νά τοῦ …… Ὅταν μιά φορά πῆγε στήν ἐκκλησία νά λειτουργηθεῖ, ἐκεῖ πού ἔπαιρνε τό ἀντίδωρο ἀπό τό χέρι τοῦ …… ἔπεσε τό …… κάτω. Σκύβει νά τό πάρει, δέν τό …… πουθενά. Ὅταν ξαφνικά βλέπει μιά μέλισσα μέ τό …… στό στόμα νά πετᾶ ἔξω ἀπό τό …… Βγάζει τότε διαταγή ὅποιος ἔχει ……	When the Emperor Justinian decided to build the …… …… in ……, no master …… present him with a sketch he …… One day, he went to church to attend Mass. While he was taking the holy bread from the hand of the ……, the …… …… fell down. He kneels to take it, he does not …… it anywhere. Suddenly, he sees a bee with the …… …… in its mouth flying out the …… He then issues an order for all bee-keepers to harvest their …… and find the holy

νά τά τρυγήσει γιά νά βρεῖ τό ἀντίδωρο. Κανένας ἄλλος δέντό ..... παρά μόνον ὁ πρωτομάστορας, πού σέ μιά ..... εἶδε ἀντί γιά κερήθρα, μιά πανώρια ..... πελεκητή καί πάνω στήν Ἁγία ..... τό ..... Αὐτήν τήν ἐκκλησιά παρουσίασε ὁ ..... στόν ..... καί ἴδια μέ αὐτήν ἔκαναν τήν	bread. It was only the chief master who ..... it; he saw a magnificent carved ..... instead of a honeycomb in a ....., and on top of the Holy ..... there stood the .... This was the church which the .... presented to the ..... and .... was made just like it. (❋)

❋1 It should be noted that the English version of the text is provided here for comparative and explanatory reasons. It is under trial period, susceptible to change, and should not be employed for screening purposes until it has been officially tested and published by the authors.

*2 Being part of the folk tradition, the legend was handed down from generation to generation and can be found in different versions in the modern Greek literature. The legend-test is cited as an integral part of the oral folk tradition of the Sterea Ellada region.

It is an open-response test. The examinee is asked to answer based on personal information and the context. Some of the questions are easy (all of the examinees can answer them, apart from those experiencing severe cognitive disorders). There are also questions which can be rather successfully answered by examinees with normal cognitive functions.

Gap filling was chosen because it is less time-consuming and features high reliability and content validity during rating.

Subjects, Materials and Methods

The HAST was administered to a sample of 567 individuals, aged 55+, as part of the primary memory disorders screening in the Ilion Municipality of Attica (see Table 2). All participants lived independently in the community and were aware that this test was experimental at the time. Additionally, for the detection of major NCDs the following scales were administered: the Mini Mental State Examination (MMSE) [Folstein et al, 1975]; the Modified Mental State Examination (3MS) [Teng & Chui, 1987]; the Clock Drawing Test (CDT) [Shulman et al, 1986].

The reference scale used was the MMSE, a 30-item screening test, whereby high scores indicate better cognitive functioning. It takes 5'-10' to administer and it has been standardized for the Greek population [Fountoulakis et al, 2000]. The authors set 23/24 as the cutoff point for the diagnosis of dementia. The MMSE assesses the following cognitive functions: a) orientation in time (items 1-5); b) orientation in space (items 6-10); c) registration (items 11-13); d) calculation (items 14-18); e) recall (items 19-21); f) language (items 22-29); and g) praxis (item 30).

***Table 2**. The socio-demographic characteristics of the sample.*

	n=	%	Mean.	SD	Median
AGE - SEX	579	100	71,1	7,2	71

Age♂	204	35,5	73,9	6,8	74,5
Age♀	375	64,9	68.9	6,9	69
55-59	32	5,5			
60-64	81	14			
65-69	130	22,5			
70-74	139	24,1			
75-79	122	21,1			
80-84	56	9,7			
85+	17	2,9			
EDUCATION	576	100			
Illiterate	26	4,5			
<Primary School	123	21,4			
Primary School	278	48,3			
<Junior High School	56	9,7			
Secondary Education	55	9,5			
Higher Education	35	6,1			
TESTS					
MMSE	566	100	25,56	3,35	26
3MS	490	100	82,65	9,8	84
HAST	566	100	67,37	10,3	70

Results

The exploratory factor analysis revealed 5 factors with eigen value higher than 1. This distribution accounts for the 5.19 of the variance. The eigenvalues of the principle component analysis were: f1=5.944, f2=1.583, f3=1.392, f4=1.198 and f5=1.122. After rotation each eigenvalue accounted: f1 15.7% of the variance, f2 12,8%, f3 11.2%, f4 8.4% and f5 7.8%. The factor loadings are calculated by applying the Kaiser Normalization Varimax. The 5 revealed factors (Table 3) account for: f1 space-temporal orientation, f2 complex intellectual skill, f3 simple intellectual skill, f4 semantic memory and f5 comprehension and content definition.

The HAST, differs from the other screening tests whose items correspond to diagnostic criteria and are allocated to independent principle components. In the HAST, the conceptual consistency of the text allows us to focus “microscopically” (zoom in) on the previously mentioned 5 factors. Macroscopically (zoom out) in the broad context of conceptual relevance of the words-items in the text, we noticed that for the successful completion of the entries 7, 12, 17 short-term memory recall is necessary (while for the entries 16, 18, 19, 20 delayed recall is required).

Finally, the set of words to be filled in requires the operation of episodic memory - as 5’ pass from dictation to text completion - encoding (natural, semantic, phonological and functional) features and recall of the stimulus. Therefore, it is episodic memory which could be considered as the central variable comprised of all 20 entries.

The reliability analysis for the total 20 entries (Cronbah’s) α=.860 (n=567) varies at a satisfactory level.

The correlation check result (Pearson’s r) with the MMSE scale yielded r=.447, while the corresponding control on the 3MS was r=.516 and for the CDT it was r=.318 ($p<0.001$).

The convergent validity of the HAST is expressed by the high correlation of Pearson’s product with the 3MS. Both scales examine the orientation in space and time, immediate and delayed recall,

critical ability, and common human experiences. The divergent validity is reflected in the Pearson test product between HAST and mainly because the later assesses visuo-constructional skills. The fact that both scales concurrently examine short term memory, comprehension, abstract thinking [Freedman et al 1994] and common human experiences justifies the relatively small deviation in the Pearson test result.

The Receiver Operator Characteristic Curve (ROC) analysis of the HAST screening value with the MMSE 23/24score [Fountoulakis et al. 2000] as gold standard, yielded an area under the curve (AUC =.773).

Sensitivity and specificity for 65/80 performance was .636 / .778, (hypotenuse (hy)=.426); for 66/80 performance it was .698 / .744 (hy=.395); for 67/80 performance it was .721 / .721(hy=.394); for 68/80 performance it was .767 / .673(hy=.401); for 69/80 performance it was .783 / .613(hy=.443). Selection scales need to be highly sensitive so as to detect people at risk to the possible extent [Moriatry, 2002]. The low sensitivity and specificity indications with respect to the MMSE can be interpreted as a bad omen, because the MMSE is widely used with high specificity and sensitivity in clinical studies. On the other hand, it has been criticized for falsely positive high rates in community studies [Mitchell, 2009]. Therefore, the standardization of the HAST scale in a community population with the use of clinical examination (in addition to other screening tests), may better substantiate its power or weakness in the detection of major NCDs. What is further attempted is the exhaustion of possibilities which the modification of the scale scoring provides through the use of linguistic features, in order to increase its sensitivity and specificity.

Although the Modified MMSE (3MS) examines (in addition to MMSE): (a) delayed recall, (b) verbal flow, (c) critical ability to provide better information, and in this case the ROC product gave: AUC = .802 and for performance a) 66/80 in the HAST, sensitivity .732 and specificity .771 (hy = .352), b) 67/80 in the HAST, sensitivity .779 and specificity .730 (hy = .348), c) 68/80 in the HAST, sensitivity .805 and specificity. 674 (hy = .379), the MMSE was chosen as the reference scale for this preliminary study because the MMSE is standardized for the Greek population and is widely used both in the daily clinic practice as well as in epidemiological and clinical studies.

Table 3*. Factor loadings, rotation component matrix and test for reliability for each factor*

		factors					Reliability analysis
ΛΗΜΜΑΤΑ	ITEMS	1	2	3	4	5	Alpha(α)
1.Κωνσταντινούπολη	3.Constantinople	.518					.829
2. Αγία	1. Hagia	.839					
3. Σοφία	2. Sophia	.895					
19. Αγία	19. Hagia	.666					
20. Σοφία	20. Sophia	.704					
10. Παράθυρο	*10. window*		.517				.704
11. Μελίσσια	*11. beehives*		.455				
13. Κυψέλη	*14. beehive*		.405				
14. Εκκλησία	*13. church*		.628				
17.Πρωτομάστορας	*17. chiefmaster*		.703				
18. Αυτοκράτορα	*18. Emperor*		.606				
6. Πατριάρχη	*6. Patriarch*			.512			.643
7. Αντίδωρο	*7. holy bread*			.680			
8. Βρήκε	*8. find*			.600			
9. Αντίδωρο	*9. holy bread*			.683			
15. Τράπεζα	*15. Altar*				.810		

16. Αντίδωρο	*16. holy bread*				.781		.684
4. Μπόρεσε	*4. could*					.805	.525
5.Αρέσει	*5. liked*					.585	
12. Βρήκε	*12. found*					.431	

F1= space-temporal orientation, F2= complex intellectual skill, F3= simple intellectual skill, F4= semantic memory, F5= comprehension and content definition.

Discussion

Major NCDs elude proper diagnosis. Two thirds of dementia cases remain undiagnosed [Larson, 2003]. Although both people and experts are being quite informed, a large number of older adults show reluctance to contact mental health professionals. Various factors account for that. Low familiarity with neuropsychological tests increases mistrust rendering them defensive. The people surrounding the patient experience a similar reluctance under the threat of the diagnosis, the stigma, or because of the mistaken attribution of the symptoms to age. Older adults often deny facing problems when dealing with difficult situations in their lives. The hitherto inability to determine functional (in vivo) pathogenic biomarkers of cognitive disorders in the elderly has incited professionals to approach them through behavioural changes in cognitive functions for population screening [Riccie & Kildea, 1995]. Primary care physicians and other trained professionals are thus required to administer screening tests in the daily clinical practice aiming at the early detection of mental disorders.

Creating an attractive test increases the chances for the elderly (or people of their entourage) to be examined, providing a first insight into their situation. Moreover, to some extent, it may mitigate the defenses against the process and the examiner, while reducing the tendency to withdraw from the effort to complete the test. The control over cognitive functions becomes a challenge to be met. At the same time, we aim to create a test which can be administered by a member of the patient's environment and, even more so, self-administered. Consequently, the mental functions of more people would be even roughly assessed, without any financial cost.

The evaluation of cognitive functions disorders through the HAST is solely based on the use of speech (oral and written). The similes and figurative speech, the verbal linkage and the implied information are all contextualized or part of prior knowledge, creating difficulties during its reproduction. Ageing, apart from the various changes in physical and psychomotor functions, causes changes in speech as well. The lexicon is among the first to be affected, as it the case with the reduced ability to learn connotations [Obler & Albert, 2006]. Conversational vocabulary diminishes as compared to comprehension vocabulary and naming skill. Phonology is spared in the third age, with variations observed at low frequency words. The decreased perception of spoken language probably reflects the increased time required for information processing [Benson & Ardila, 1996]. Age does not negatively affect grammar (morphology and syntax), but there is difficulty in understanding complex syntax. When mnemonic load does not occur, normal older adults perform well in subordinate sentences or additional clauses. Naming skill is reduced, while the verbal linkage in the mental lexicon weakens over the course of years or due to lack of use, particularly true of words without rich semantic connections. The difficulty mainly lies in word identification and word retrieval rather than in the mnemonic loss of information [Tsantali, 2005].

Reaching beyond the rigid accuracy of diagnostic criteria, the structure of the HAST permits to

investigate the orientation in space and time, trail making and information recall (immediate and delayed), semantic memory, simple and complex reasoning ability, abstract thinking, and the use of grammatical and syntactic rules.

The administration of the HAST constitutes an open challenge, considering the recent interest in the creation of new or the conversion of in-use scales and tests electronically. The saving of time, cost reduction, the accurate recording of test responses and the automatic storage with the possibility of comparison (with the re-administration or other scales administration) are some of the key advantages of electronic versions. Nonetheless, what is of paramount importance is that these e-tests can be administered by other medical specialties and professionals who are not highly trained, such as nurses or other mental health professionals [Zygouris & Tsolaki, 2015]. The analysis of the test by means of human and artificial intelligence may contribute to the clarification of its psychometric and psycholinguistic features, which compose the (capacity) algorithm of the screening test. This could possibly lead to the creation of a model of features for the production ofrelevant culturally oriented tests (for other populations) for the detection of major NCDs.

Conclusion

The objective is for the HAST to constitute an early detection tool based on the mitigation of the inhibitions of the elderly (and their relatives) to be examined, its usability, and easy access to anyone wishing to use it.

The electronic administration and performance rating of the elderly will help to reduce the arbitrary interpretation bias of test answers by the examiner, considering that the means for the evaluation of cognitive function disorders is the use of speech.

The online database will be informed with the test data, along with data collected from a large part of the population, since the administration, evaluation and results sharing among health professionals will not require professional intervention.

Should the specific test prove to be adequate for the detection of major NCDs and complement the existing ones, it is expected to contribute to the increase in the number of the elderly examined on an annual basis, to the decline of undiagnosed cases, and ultimately to the early detection and increase in the percentage of elderly people who receive opportune treatment.

Future directions

It is worth studying whether, a friendly screening test, easily accessible to family members (son, daughter, spouse of the elderly), who may administer it using an electronic device (tablet – smartphone – PC), and which will automatically rate and store the results on an online contact channel (cloud) of graded access, will actually increase the number of older people who will be examined primarily and secondarily by a memory clinic specialist (if the first examination has an indication for further testing).

All authors declare that they have no conflicts of interest.

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Gender differences in senile depression. Ilion Municipality Hellenic Study (I.M.H.S.)

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Abstract

Introduction: Depression is a disorder with a high prevalence among older individuals. Specific genotypic expressions, loneliness, various types of loss, cognitive decline, and psychosocial adversities are commonly considered as risk factors. Also, women have been steadily related to accentuated risk for the development of depression. Scope: (a) estimation of the frequency of depressive symptoms in female and male older individuals, (b) exploration of the role of socio-demographic factors in the development and severity of depressive symptoms, and (c) detection of differences on the patterns of depressive symptoms according to gender. Methods: A cross-sectional study including 358 participants over 60 years of age was conducted. Females and males were matched for age. All participants were community-dwelling older adults. The Geriatric Depression Scale short form (GDSsf) was applied for the evaluation of depressive symptoms. Results: The odds ratio of females to males for the development of depressive symptoms was 1.81. The GDSsf scores of 5% of males and 6.7% of females indicated moderate to severe depressive symptoms (M.-S.D.), whereas the GDSsf scores of 16.8% of males and 26.8% of females indicated mild to moderate depressive symptoms (M.-M. D.). As far as the males are concerned, the chi-square test for independence showed that M.-M.D. was significantly associated with age, education, traumatic experiences and marginally with living alone. In the case of females significant associations were observed with physical exercise and the presence of grand-children. Finally, in the female group M.-S.D. was associated with the amount of leisure activities. At a qualitative level, males where characterized to a greater extent by feelings of hopelessness whereas females by apathy. Conclusion: The high frequency of depressive symptoms in older females compared to males could be explained, apart from gender-related biological differences, by socio-cultural factors that prevent women from achieving mastery or high levels of self-worth, thus leading to dependency, low self-esteem and finally to depression. The detection of various protective and risk factors as concerns the presence of depressive symptoms might add to the existing knowledge and facilitate the application of effective intervention programs that focus on improving the psychosocial health of older adults.

Introduction

Depression is a disorder with high prevalence among older individuals. Genetic factors, the pathological load, cognitive decline, an amount-of any kind-of losses [1-12] and psychosocial adversities [2,13] create the conditions in which depression thrives.

According to the WHO, depression constitutes the main cause of disability worldwide and is one of the key components of the disease burden globally. About 1-4% of elderly people suffer from major depression [1,6,9,14]. This percentage is equivalent to an incidence of 0.15% cases per year. Nevertheless, only a small proportion (5-10%) who make use of primary care services report clinically significant depressive symptoms [15]. The under-diagnosis and under-treatment of the disease may be due to a combination of the following reasons: the specific clinical and phenomenological signs of senile depression; the prevailing negative stereotypes concerning ageing and mental disorders, both in the general population and among specialists [16]; the intrinsic difficulties in the effectiveness of liaison psychiatry.

Women are more prone to develop depression. Maybe this is one of the most robust findings in the psychiatric epidemiology [6,14,17-20], both in clinical and in community studies. This phenomenon is observed regardless of region, assessment tools and diagnostic models [21]. Further study of the bio-psycho-social factors may indicate their role in this phenomenon, as well as the way these factors interact. Although several interpretations have been considered and discussed, none of them has been able to offer a sufficient explanation [22].

As regards the Greek population (table 1) the studies by Papadopoulos et al[11], Argyropoulos et al[12], Argyriadou et al [23], Stylianopoulou et al [24], and Carayanni et al [25] are based on the Geriatric Depression Scale short form (GDSsf) [26]. The Madianos et al.[10] study is based on an assessment scale (CES-D) [27] and additional clinical evaluation. There are few other differences in methodology observed. Although the GDSsf is validated for the Greek population [28] there is inconsistency in the use of cut-off scores and sample age. The depressive symptoms ratio among men and women ranges from 1/1.21 to 1/1.55. In the study by Papadopoulos et al[11] the odds ratio for women to develop depression is 1.29.

***Table 1**: Senile Depression studies in the Greek population*

Authors -Year	Area	Assessment	Sample n / age	Prevalence / sex	Prevalence
Madianos MG. et al., 1992	Athens urban area[1]	CES - D cut off ≥ 16 & DSM-III criteria	n=307 65+ y.o..	♂ 8,4% ♀ 10,2%	27,1% Depressed By applying diagnostic criteria 9,5% affective disorder
Argyriadou S. et al., 2001	Chrisoupolis Thessaloniki Suburban Area[2]	GDSsf Cutoff ≥5	n= 536 65+y.o.	♂ 19,6% ♀ 29,9%	20.9% depressed
Papadopoulos FC. et al.,2005	Velestino Thessalia Rural Area[1]	GDSsf Cutoff Mild depr ≥7 severe ≥ 11	n=608 60+y.o..	♂ reference ♀ 1,29 O.R	Depression Mild 27% Severe 12%
Stylianopoulou Ch et al., 2010	Agioi Anargyroi Attika Suburban Area[1]	GDSsf Cutoff Mild depr ≥7 severe ≥ 11	n=360 60+y.o..	♂ 29,4% ♀ 70,6%	30,28% depression Mild 22.22% Severe 8,06%
Argyropoulos K. et al., 2012	Patras Urban Area[1]	GDSsf Cutoff Mild depr ≥6 severe ≥ 11	n= 239 60+y.o.	♂ 37,4% ♀ 54%	36% moderate depression 9,2% severe depression
Carayanni V. et al., 2012	Agioi Anargyroi Attika Suburban Area[1]	GDSsf cutoff 6/7	n=359 60+y.o.	♂ 22,53% ♀ 35.12%	30.3% depressed

1. Community Dwellers, 2. Health center - Retirement / Elderly care - Open Centre for elderly

Hypotheses:

One of the most robust and well documented findings in epidemiology is the higher depression rate in women [6, 9, 21, 29]. Does the severity of depression follow this pattern? Do specific socio-demographic factors affect both sexes equally? Does the depressive symptoms as depicted in the screening tool follow the same pattern for both sexes? The aim of this study is to answer the above questions.

Materials and methods

A cross sectional study was conducted involving a total of 358 individuals over 60 years of age (table 2). All individuals, who participated voluntarily in the study, live independently in an urban area of the Attica region.

Table 2: *The socio-demographic characteristics of the sample.*

TABLE2	TOTAL N=	%	MALE n %		FEMALE n %		Mean	S.D.	Median
SEX	***358***	*100*	n=179	50%	n=179	50%			
AGE	***358***	100					**73,58**	**5,84**	**74**
Age ♂			**179**	**50%**			**73.63**	**.437**	**74**
Age ♀					**179**	**50%**	**73.54**	**.438**	**74**
60-65	30	8,4							
65 – 69	56	15,6							
70 – 74	102	28,5							
75 – 79	116	32,4							
80 – 84	46	12.8							
85+	8	2,2							
EDUCATION	***358***	**100**							
ILLITERATETE	16	4.5	6	3.4	10	5.6			
ELEMENTARY<	72	20.3	27	15.2	45	25.4			
ELEMENTARY	172	48.5	85	47.8	87	49.2			
HIGH SCHOOL<	41	11.5	24	13.5	17	9.6			
HIGH SCHOOL	32	9	19	10.7	13	7.3			
COLLEGE – UNIV.	22	6.2	17	9.6	5	2.8			
MARITAL STATUS.	**358**	**100**							
MARRIED	235	66.4	151	85.3	84	47.5			
WIDOWED	104	29.4	20	11.3	84	47.5			
DIVORCED	9	2.5	2	1.1	7	4			
SEPARATED	3	0.8	2	1.1	1	0.6			
UNMARRIED	3	0.8	2	1.1	1	0.6			
SOLELY LIVING	**358**	100							
YES	**88**	25.1	23	13.2	65	36.7			
NO	**263**	74.9	151	86.8	112	63.3			
GDS SCORE	**358**						**4.08**	**3.29**	**4**
GDS score ♂							**4.19**	**3.22**	**4**
GDS score ♀							**5.41**	**3.27**	**5**

The distribution of participants in the age groups was equal for both sexes in order to avoid the risk of bias effects [1,6,9], because of the difference in the mean age among men and women (74.68 and 70.91 respectively) in the total sample.

The socioeconomic status of the participants was characterized as low, taking into consideration

their educational level and the occupation they practiced before retirement. The majority of them (60.2%) grew up in small rural communities, while 66.1% were raised in families who lived in poverty and struggled to cope with the basic survival needs. However, they still characterized their families as affectionate (52.7%) rather than absorbed by harsh circumstances (42.4%). The families were large, as each family had an average of 5.17 children (s.d. 2.31). Concerning their place of origin, according to our data: 62.1% grew up in villages, 8.5% in towns, 12.7% in cities and 16.7% in urban centers. As far as the educational level of the participants is concerned, 4.5% were illiterate (3.4% ♂, 5.6% ♀), 20.3% did not complete primary school (15.2% ♂, 25.4% ♀), 48.5% graduated from primary school (47.8% ♂, 49,2% ♀), 11.5% did not complete high school (13.5% ♂, 9.6% ♀), 9% graduated from high school (10,7% ♂, 7.3% ♀) 6,2% were higher education graduates (9,6% ♂, 2.8% ♀) .

Regarding the occupation of the participants, according to our data: the majority i.e. 49.6% (57.8♂, 41.2% ♀) were manual workers, 11.1% (12.1♂, 10% ♀) were employed in jobs that required intellectual skills, 7.9% (11.6% ♂, 4.1♀) were merchants, 22.2% were housewives (0% ♂, 44.1% ♀), and 9.3% were employed in a different professional activity (17.9% ♂, 0.6% ♀).

Exclusion criteria: a) people supported by carers, community or institutional structures; b) participants who scored below 18 on the MMSE scale. We followed DeCraen et al [30] and Marc et al [31], who in their studies excluded participants with MMSE performance <18. The reason was the questionable credibility of the GDSsf in the detection of depressive symptoms in elderly with moderate to severe dementia due to the cognitive decline and / or the difficulty of the participants in insight and emotion description.

The GDSsf is a generally accepted reliable tool for depression screening, validated in many countries and used both in everyday clinical practice and epidemiological studies [32-34]. The 15 items of the scale do not assess physical and neurodegenerative factors, which overlap with symptoms of concomitant physical disease [35]. The GDSsf was translated into Greek and validated by Fountoulakis et al [28]. The authors set the cut-off point at 6/7 for the distinction between depression and non-depression. The short time (5') of the scale administration minimizes the risk of fatigue, disrupted concentration and attention, especially in those individuals with physical illnesses and memory deficits [36], who tend to give inaccurate responses when tired. Although the scale is self-administered, in the present study it was administered by an examiner.

The GDSsf derives from the extensive 30-item GDS[37]. Adams[38] and Cheng & Chan[39] in their studies revealed 5 principle components, including: a) Dysphoria (items 1,3,4,6,11,15), b) apathy, withdrawal, lack of vigour (items 2,9,13), c) hopelessness (5,8,12,14) d) anxiety (7) and e) memory (10). Sheikh and Yesavage [40] in their study concerning the 30-item GDS also pinpoint 5 factors: 1) sad mood and pessimistic outlook, 2) mental and physical energy, 3) positive or happy mood, 4) agitation or restlessness and 5) social withdrawal. In this factor analysis 4 items of the GDSsf are not included. It is considered more efficient to use as gold standard the convergent studies of Adams [38]and Cheng & Chan[39].

Additional socio-demographic data, including sex, age, education, time and place of birth, occupation, family status, solely living, presence of children and grandchildren, leisure activities, physical exercise, were collected.

The IBM SPSS v.23 and descriptive analysis were used for the purposes of this study. The

sample was not normally distributed (Kolmogorov - Smirnov's p <0.001). Non-parametric tests (Mann – Whitney or Cruskal – Wallis) were conducted in order to explore the effect of socio-demographic characteristics on the GDSsf scores for both sexes.

Furthermore, a chi-squared test (x^2) was conducted in order to examine whether there was statistical significant independence between the categorical variables: a) the severity of depressive symptoms according to the GDSsf performance and b) the socio-demographic characteristics.
Using Sperarman's product (rho) the correlations between sex and the examined phenomenology of the depression according to the GDSsf were estimated, organized in item groups, and in a graph showing the severity of depression for men and women based on the mean GDSsf item scores.

Results

The Cronbach's alpha product for the GDSsf indicated that the reliability and consistency of the GDSsf scale was sufficient (α= 0.775 / n=358).
Applying the 6/7 cut-off score [28], 21.8% of the male and 33.5% of the female participants were found to experience depressive symptoms. The x^2 test indicated that the categorical variables were dependent. Particularly, the odds ratio for women (vs. men) to develop depression was 1.81. As a measure to estimate the severity of depressive symptoms, the cut-off scores proposed by Papadopoulos et al. [11] were used: scores 7-10 correspond to mild to moderate depression (M.-M.D) and scores 10-15 correspond to moderate to severe depression (M.-S.D).

With respect to the severity of depressive symptoms, 5% of male and 6.7% of the female elder individuals scored between 10 and 15, so they fell into the category of M.-S.D. The x^2 test showed that the variables were independent [$x^2(1, n=358) =.97, p>0.05$]. Furthermore, 16.8% of the male and 26.8% of the female participants obtained scores that corresponded to M.-M.D. The x^2 test showed that the variables were dependent [$x^2(1, n=358) =5.83, p<0.05$].

The non-parametric testing (Table 3) for the effect of socio-demographic factors on the performance of the participants on the GDSsf scale showed that:

a) For the male participants, the following variables had an impact on the performance on the GDSsf: age (p =0.002), traumatic life event (p =0.031), spouse existence (p =0.008), living alone (p = .000), physical exercise (p = .010) and marginally education (p = .052).

b) Accordingly, the variables influencing the performance of women on the GDSsf were: the presence of grandchildren (p = .016) and physical exercise (p = .001)

The x^2 test between (Table 3):

1) M.-S.D. and: age, education, occupation, place and season of birth, traumatic life event, spouse existence, solely living, physical exercise, and memory disorders showed that the variables were independent for both sexes (p>0.05). Leisure activities were found to be a dependent variable for women [$x^2(1,n=179)=14.80, p<0.05$].12% of women who spent their time in "passive type" activities (such as watching television) and 50% of those who reported no leisure activities suffered from M.-S. D.

2) M.-M.D and the socio-demographic factors (Table 3) showed:

A) For the male elder individuals, age [$x^2(1,n=179)=8.10$, $p<.05$], education [$x^2(1,n=179)=6.06$, $p<.05$], season of birth [$x^2(1,n=179)=16.12$, $p\leq.001$], traumatic life event [$x^2(1,n=179)= 34.12$, $p<.05$], and marginally living alone ($p=.053$) were dependent variables

B) For the female elder individuals, the presence of grandchildren [$x^2(1, n=179)=7.56$, $p<.05$] and physical exercise [$x^2(1,n=179)= 10.00$, $p<.05$] were dependent variables. 23.7% of women who had grandchildren obtained scores that corresponded to M.-M.D versus 48.4% of those without grandchildren.

***Table 3**: Non parametric and chi square (x^2) tests between depression and socio-demographic variables.*

TABLE 3		TOTAL SCORE GDSsf		Moderate to Severe Depression (score11-15)		Mild to Moderate Depression (score7-10)	
VARIABLE		U	P value	X²	P value	X²	P value
AGE <74 / 75+ years	♂	5.085,5	**.002**	2.198	.173	8.108	**.005**
	♀	4.425	.212	.018	1.0	2.936	.091
EDUCATION ≤5/6+years	♂	1877	.052	2.311	.147	6.066	**.032**
	♀	2961.5	.210	.096	.747	.644	.461
OCCUPATION	♂	4.299	.365	1.174	.759	6.733	.151
	♀	3.417	.556	2.307	.679	.596	.964
BIRTH SEASON	♂	6.303	.098	4.904	.179	16.122	**.001**
	♀	1.376	.711	.654	.884	1.274	.735
PLACE OF BIRTH	♂	.625	.891	5.327	.149	1.720	.633
	♀	3.530	.317	2.816	.421	.822	.844
LIFE TRAUMATIC EVENT	♂	28.097	**.031**	14.316	.502	34.124	**.005**
	♀	8.916	.710	10.455	.490	7.496	.823
SPOUSE	♂	2.777,5	**.008**	2.928	.116	2.162	.158
	♀	4.470,5	.163	.334	.763	2.009	.173
SOLELY LIVING	♂	2.536,5	**.000**	4.860	.062	4.770	.053
	♀	3.932,5	.371	.228	.753	.469	.591
CHILDREN	♂	425.5	.986	.340	1.0	1.129	.587
	♀	530	.124	.524	1.0	1.220	.273
GRANDCHILDREN	♂	3.140	.365	.178	.705	.606	.497
	♀	1.704	**.016**	.252	1.0	7.568	**.008**
LESURE TIME ACTIVITIES	♂	6.922	.328	5.996	.424	9.214	.162
	♀	11.327	.079	14.808	**.022**	9.030	.172
PHYSICAL EXERCISE	♂	2.673,5	**.010**	1.098	.312	1.719	.263
	♀	2.353,5	**.001**	2.865	.108	10.009	**.002**

Age seems to affect the male and the female participants in a different way. Particularly, in ages less than 74 years, the frequency of M.-M.D. in women was found to be at higher levels (23%) than in men (9.9%). After the 75th year, while for women the frequency of M.-M.D showed a slight increase (35%), for men it almost tripled (26.6 %). Respectively for the M.-S.D., the frequency in women <74 years was 9.5% which was significantly higher than the respective in men (3.5%). After the 75th year, the frequency of M.-S.D. was reduced for women to 8.8%, whereas for men it attained 9.4%.

The educational level in the sample showed a wide disparity, as 18.5% of men versus 31.1% of women had a mean education of <6 years. The independence test indicated that education and both M.-M.D. and M.-S.D. were only dependent for the male participants (p <.05), whereas the variables were independent as concerned the women. The odds ratio (O.R.) to develop M.-M.D for men with education <6 years compared to those who had 6+ years was calculated to be 2.9; the O.R for women was 1.3. Respectively, the O.R. to develop M.S.D was 2.9 for men and 1.2 for women (95% confidence interval). Men and women who were employed in intellectually challenging posts showed lower rates of depression compared to other categories.

Regarding marital status, the ratio of lone men aged <74 to women was 1 / 4.9 (♂ 9.6%, ♀ 41.5%) while for those over 75 years the ratio was 1 / 2.94 (♂ 22.4%, ♀ 65.9%). The frequency of M.-S.D. was 4% in married men and 8.3% in married women. The frequency of M.-S.D. was 15% in widowers and 4.8% in widows. The frequency of M.-M.D. was higher in women, in all these categories.

The ratio of lone men aged <74 to women was 1 / 2.94 (♂ 9.9%, ♀ 28.7%). For the 75+ year-olds, the ratio was 1/2.71 (♂ 16.9%, ♀ 45.8%). The odds ratio to develop M.-M. D. was 3.01 for lone men vs. 1.27 for women whereas for M.-S.D it was 4.73 vs. 1.34, respectively.

The correlation (Spearman's -rho- product) between the depression relevant scores of the male participants and parameters such as dysphoria (ρ = .656, p<0.001), apathy (ρ = .373, p<0. 05), hopelessness (ρ = .597, p<0.001) was statistically significant, while anxiety and memory difficulties (as reflected in the 7th and 10th questions of the test) did not show any statistically significant correlation [(ρ= -. 083, p>0.05), and (ρ= .167, p>0.05) respectively]. For women, the correlation between their performance and the parameters such as dysphoria (ρ= .645, p <.001), apathy (ρ= .488, p <.001), hopelessness (ρ= .495, p <.001), anxiety (ρ= .351, p=.006) was statistically significant, whereas memory disorders showed no significant correlation (ρ= .140, p>0.05).

The mean scores of the GDSsf principle components as they are depicted on the graphs show that men with M.-S.D. were rather dominated by the feeling of hopelessness while women showed higher levels of distress, apathy and anxiety (Figure 1). The same pattern was repeated in M.-M.D. but with significantly smaller deviations (Figure 2). The non-parametric test showed that sex did not affect the severity of symptoms (p> .05) in subjects with M.-M.D. and M.-S.D.

Figure 1: Depressive symptoms in M-S depressed elders

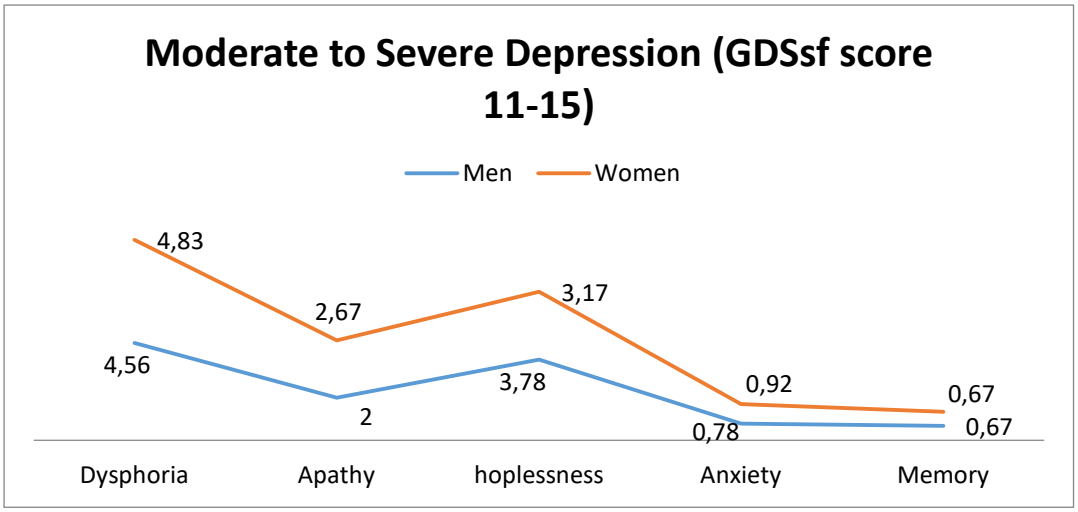
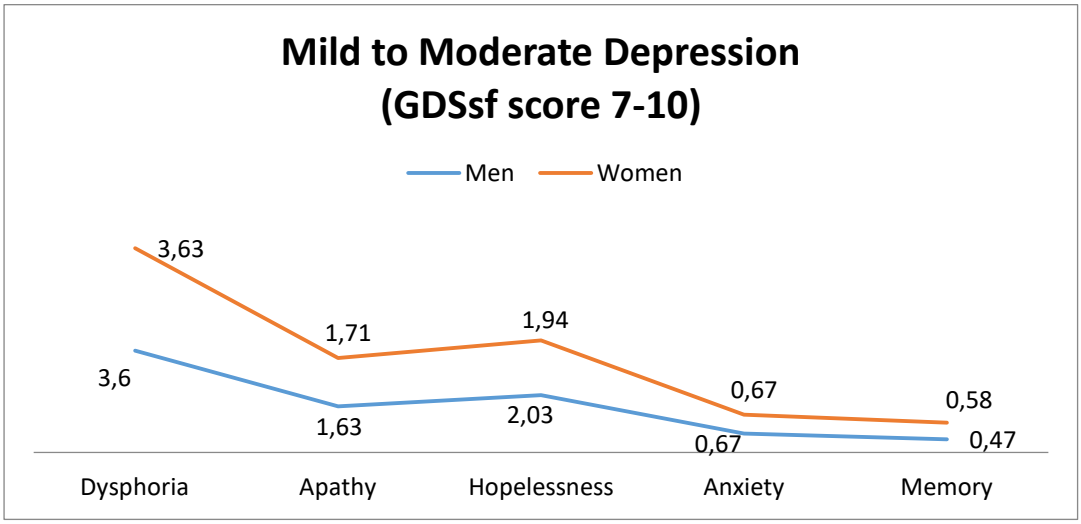


Figure 2: Depressive symptoms in mild-to-moderate elders



Discussion

According to the GDSsf performance, a significant proportion of the assessed population appears to have depressive symptoms. The frequency in women is higher than in men.

In the present study, in accordance with the results yielded by Papadopoulos et al [11] there is no statistical significant difference between males and females concerning M.-S.D. Female preponderance in depression constitutes a phenomenon which many researchers worldwide have been trying to explain. Myrna Weissman [41] concluded that women's propensity to seek medical help or men's propensity to alcohol abuse or anger outbursts is not an artifact. The biologically oriented approach is widely accepted as genuine and robust[21]. Also genuine and robust are the patterns of long-lasting and global discriminative behavior patterns against women which are depression-genic. The disadvantaged social status of women could explain the differences in the frequency of depression between the two genders [41].

Various studies [6,9-11,23,42] concerned with the influence of the age variable in senile depression highlight the 75th year as a threshold. In the present study, even though M.-M.D. slightly increased

after the 75th year, M.-S.D. is at a lower level than men, in whom the frequency doubles.

The findings of the present study corroborate other research findings concerning the higher rate of female cognitive impairment and disability [9, 17, 43] attributed to higher life expectancy [44], the subsequent health fragility and the psychological consequences due to loss experience during their lifetime[1]. The lower rate of women suffering from M.-S.D. vs. men in the present study differentiated of the Demura & Sato[45] study who observed a higher proportion of major depression in women aged over 75 than in men.

The majority of female participants were married. This tendency was also observed by Laidlaw et al[46]. The gender-attributed role of women to be responsible for household issues, after marriage, includes taking care of the husband. The age difference between spouses increases the possibility for men to develop (first) age related illnesses which renders their (in most cases weak) autarchy in daily life demands weaker. In parallel women are more likely to shoulder the caregiver burden. This condition nests fragility to develop affective disorders, underlies health problems and degrades the quality of life [25, 47-51]. The majority of elder female individuals take care of their grandchildren who are highly demanding subjects, like their husbands but in a different way. This kind of care has the opposite effect compared to the care of the husband. Indeed, grandmothers seem to be protected against M.-M. D compared to women without grandchildren. Budini-Gattai & Mousatti[52] underlined that being a grandchild carer is a significant psychological experience with significant impact on the relationships with other family members. Eisenberg [53] noted that maternal grandmothers are strongly attached to their grandchildren because of their availability while Carayanni et al [25] pinpointed the protective role of the care of grandchildren.

Married men are less M-S. Depressed than widowed ones while married women seemed to be more prone to M.-S.D. Most women seem to have lost their spouse under the age of 75, mainly due to the lower life expectancy of men and the usual age difference between spouses. The long period of grieving allows its gradual resolution and consequently the better adjustment to the new situation, which is reflected onto the lower (according to this interpretation) rate of depression development.

Many of the women who participated in the present study had not worked outside the home or worked at family enterprises without insurance or wages, and on the whole, they had undertaken the household and domestic responsibilities. The loss of the husband led to financial independence for many of them. Demura S. and Sato [45] referred to the beneficial effect of financial independence and the consequent feeling of pleasure in depressed elderly women, while Hessler [44] refers to the sense of limited autonomy due to financial dependence.

The lapse of time between the loss of the husband due to the age difference between spouses, the release from the care burden and the financial autonomy, counterbalance the loss especially after the resolution of grieving. These factors contribute to adjustment and affect the mood of elder women in a beneficial way.

In our sample, lone men faced increased risk to develop depression compared to women. Lone living is more common among old women in good physical condition, as they consider it as a proof of well-being and a chance not to burden their children's families. On the contrary, men, who are less autonomous and less able to take care of themselves, especially after the loss of the spouse, join either voluntarily or necessarily their children's family or a nursing home. Djernes [6], Cole &

Dedunkuri[9] and Madianos et al[10] associated the possibility of living alone with increasing age, which further increased the possibility of depressive symptoms development.

Leisure time activities seem to influence the GDSsf outcome. Women's activities are organized around the home in contrast to men. With respect to the time dedicated to these activities on a daily basis, men try to ensure that their leisure activities will not be disturbed if possible by their daily duties, whereas women give priority to their daily duties, except for their religious practices, which are non-negotiable. Leisure activities are inextricably linked with the sense of creativity and consequently play a preventive, protective or/and restorative role in affective disorders, since they help the elderly to remain active and to reframe their social role.

Paillard-Borg et al [54] describe leisure activities as part of an active lifestyle associated with a sense of fulfillment, reduced stress and less depressed mood. Thompson [55] underlined the tendency of women to organize their activities based on their family responsibilities and Henderson et al [56] referred to female tendency to associate (unstructured) leisure activities with the home as opposed to men. Larson[57] referred to mobility difficulties and fewer opportunities to engage in such activities due to the low socio-economic status of women. Larson et al [58] pointed out that women are often unable to be carefree in family gatherings as they cannot be dissociate from the role of the caring housewife. On the contrary, they accomplish their role and experience esteem, too.

The socioeconomic status of the elder individuals who participated in the study was low, according to their educational level and occupation. Men with low educational level were at higher risk of developing M.-M.D. and M.-S.D. whereas women were not influenced. The majority of the participants were poorly educated (elementary or lower level). In this study, while the educational level is directly related to mood disorders for men, this is not the case for women. Relevant literature suggests “indirect routes” of relationship between education and mood disorders. In particular, a) years of education play an important role in cognitive disorders [5, 59-64], which occur more frequently in women [65,66]. These cognitive disorders are associated with depressive symptoms [4,6,7,9,10-12,67] b) people with low educational level have fewer leisure-time activities [68], c) there is an intercultural framework of discriminations against people with low educational level [21,41].

During the socio-demographic data interview, the participants were asked to report traumatic and/or life events during their childhood, adolescence, and adulthood particularly focusing on the last decade. Both the scale of Holms-Rahe [69] and the categorization by Sadock et al[3] do not include all the events that were reported by the participants or are weighted differently because of the differences in the temperament and social norms. However, the recording of life events in the study by Tsolaki et al [70] was almost identical with the present one. The impact of life events is fully revealed before the clinical manifestation of depression [21]. In the present study, the fact that life events influence women less can be attributed to stronger support systems. In particular, religiosity is among the protective factors. The individual “reframes” the stressful event as a challenge for their faith which gives them the opportunity for intellectual improvement. Similarly, Fountoulakis et al [71] pointed out that religion is the only factor that has a beneficial effect on depression at the after-6-month retesting and that religious patients had a broader, stable, supportive social network and better mental functioning. Hahn et al [72] like Milstein et al [73] reported the protective role of participation in religious rituals regarding senile depression. Smith et al [74] referred to the consolation

and comfort derived from the rituals and the belief that life is governed by divine providence. Miller and Hoffman [75] attribute the greater religiosity of women (compared to men) to the fact that the former were raised by the urge to be humble, submissive, and patient (the men raised according to this model are more religious too). Nonetheless Carayanni et al[25] found no significant association between weekly church attendance and depressive symptoms in either gender.

In the present study, the qualitative differences in the depressive symptoms between men and women were identified based on their performance on the GDSsf. Men were characterized by a greater sense of despair while women felt more apathetic. The withdrawal of women- either reported by themselves or observed by others- causes an intense impression to their environment. The withdrawn-depressive women do not occupy themselves with daily activities (cooking, cleaning the house). Suffering ceases to be a mute and personal affair, because it disturbs the life of the rest of the family, especially the husband. Women must undergo a lot of pressure (internal or external) before they seek help. On the contrary, depressive men of the same age go more rarely out the house, reduce their leisure activities and consequently, their depression often goes unnoticed. However, Sonnenberg et al[17] reported only quantitative differences in the performance between men and women on almost every section of the CES-D.

Limitations.

1. The absence of clinical diagnosis prevents the association of these factors with depression and reduces the validity of the findings.
2. The exclusion of elders whose daily needs were provided by other family members or community structures or who lived in nursing homes narrowed our study.
3. We did not address biological parameters which trigger depressive symptoms
4. The absence of a standardized and customized hierarchical scale of traumatic life events for the Greek population created doubts concerning the reliability of this variable in the present study. For this reason, the parameters were tested only quantitatively without a standard classification for their severity.

Suggestions for future research:

1) It is noteworthy that the frequency of depression in the present study, the Carayanni et al. [25] and the Madianos et al[10] ones is adjacent taking into account the expected impact of the economic crisis to the already shrunken income of the participants.

2) The percentage of lone elder individuals was 23.6%, whereas in the early 1970's it was 11.5% and in 1990 32.7% [10]. It would be interesting to explore whether the financial crisis led to the reduction of the rate between 1990 and the present study, as many of the participants have been supporting financially the families of their unemployed children.

3) Klerman & Weissman [76] remarked in their study that in the baby boomers cohort the frequency of depression in women tended to stabilize, while it increased in men. This phenomenon was attributed to changes (in the new generation) in the distinct roles of men and women and in the increase of working women. At the same time, early-onset depression was observed [77]. As this cohort crosses the threshold of the third age it is challenging to study the differences in geriatric depression between men and women.

Conclusion

Any attempt to content with senile depression needs to focus on the gender specific bio-psycho-social traits and the derived preclinical and clinical differences [88, 89]. In this study it was revealed that most of the variables influenced men although women are more prone to disclose their depressive mood. Gutman [78] mentioned that this phenomenon is probably related to the reversion of the emotional roles in mid-age among men and women. Women tend to be more assertive while men come closer to their sentimental self. M.-S.D. does not seem to be influenced by socio-demographic factors except for the influence of leisure time activities for women.

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Neuropricing: Perspectives of brain reactions to price exposure

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Abstract

Objectives: The purpose of this paper is to analyse existing literature and find empirical evidence regarding the effect of pricing strategies on consumer purchase decision making, both on a behavioral and a neuropsychological level, i.e. whether prices influence and correlate with human brain functioning. Methods: The paper is based on an investigation and review of studies from selective international journals dealing with pricing and its impact on consumer behaviour and decision making. Results: A series of various pricing strategies is presented, which, in total, are in a position to successfully influence consumer behaviour at cognitive, emotional and behavioral levels. Conclusion: The study confirms a complete lack of research on the effect of neuropricing on consumer behaviour and anticipates the need for the evolution of this field.

Keywords: Neuropricing - Emotions - Consumer Behaviour - EEG - Bias

Introduction

Adam Smith [1], the father of modern economics, in his famous 1776 book “An Inquiry into the Nature and Causes of the Wealth of Nations”, noted that “every man lives by exchanging”. Indeed, since the beginning of humanity, man has been dealing with some kind of merchandise and exchanging goods. Nothing much has actually changed since then, apart from the introduction of more complicated types of prices and a wider choice among customized goods and services provided on behalf of the suppliers. Teeth from whales gave way to sea shells and shinny stones gave way to modern money whereas exchanges expanded from staple goods to custom-made and luxury products.

Profit-orientated entities focus on the following three factors: cost, revenue and, of course, profit. Every economics freshman knows that in order to increase profits, one should maximise revenues and/or minimise costs. Organizations, however, do not seem to fully utilise the available academic knowledge on price setting, thus making suboptimal decisions [2]. In this way, businessmen often view pricing, despite its significance, in a rather simplistic way, more as a one-sided decision, thus missing out a basic factor, that being customer psychology.

The function of price in consumer behaviour is unquestionably powerful and complex. Consumers quite often rely heavily on price as a predictor of quality inference [3, 4], while paying less attention on, or even ignoring, other equally important aspects, such as product characteristics. Furthermore, the assumptions of quality they make on price have a significant impact on their actual buying decisions.

These assumptions, or **cognitive heuristics** as more commonly known**,** are simple mental shortcuts that explain the process by which people make intuitive judgments and come to decisions, whilst being short of adequate information. Despite the fact that these heuristics are "*highly economical and usually effective*" [5] and at times even yield positive results, the risk of leading to deviations from rationality, hence to a series of **cognitive biases**, should not be easily overlooked.

Von Neumann and Morgenstern [6] in their renowned "Theory of Games and Economic Behaviour" described consumers as rational economic actors that select alternative options with the highest expected utility or value. On the other hand, Tversky and Kahneman [5, 7] in their respectively well-known "Prospect theory" doubted this established normative view of economic decision-making, suggesting that individuals are **irrational** decision makers, often making judgments under uncertainty. The subjectivity, or irrationality, of consumers' purchase decisions are in accordance with Lindstrom and Underhill [8] and Schneider and Woolgar [9] both suggesting that customers' buying decisions are based on **emotional** rather than rational factors.

The above findings, among others, have led to the creation of **neuropricing**, a new field of marketing research that studies consumers' responses to price stimuli on a biological, cognitive, emotional and behavioral level. Neuropricing attempts to measure and predict the unbiased willingness-to-pay for products and services, avoiding explicit statements from customers, collected either by questionnaires or other conventional methods. In order to get customer feedback **implicitly** and **free of any response bias**, researchers use state-of-the-art neurophysiological measurements and methods, such as:

- **Functional magnetic resonance imaging (fMRI).** It measures metabolic activity in the brain by estimating the Blood Oxygenation Level-Dependent (BOLD) signal.
- **Electroencephalography (EEG)**. It records electrical activity of the brain with electrodes placed along the scalp. It records brain activity in emotional states such as happiness, relaxation, excitement, stress, sadness, anger etc. Many studies suggest that EEG signals "provide enough information for the detection of human emotions" [10]. In accordance with that, a recent study by Tsolaki, Kosmidou, Kompatsiaris et al [11] "investigated the response to different emotional stimuli and the effect of age on the neuronal activation", confirming that it possible to measure and process emotions by acquiring high-density EEG data.
- **Emotional Facial Recognition.** It measures the slightest expressions on the face of a subject that correspond to a wide range of different emotional states and this can be done through the use of a camera [12].
- **Eye tracking**. It measures where the subject is looking, the motion of the eyes on a stimuli and the pupil dilation [13].

The aforementioned methods help researchers explain what is happening inside a consumer's brain, or "consumer's black box" in marketing terminology, in order to learn why and how consumers make their purchase decisions. Thus, setting prices without adequate and proper research may as well result to a company losing a significant amount of sales.

The current study **aims** to identify and assess the existing literature on a wide spectrum of academic journals on issues relating primarily to pricing and consumer purchase behaviour and in extend to neuropricing and consumer purchase behaviour, in order to explore the various ways human brain reacts to diverse price exposures. This is done because "*while there are extensive theories/models of how a firm should price its goods and services, descriptive research on how firms*

make their pricing decisions is sparse in the literature" [14].

Finally, the study confirms a **gap** in the existing bibliography combining the fields of neuropricing and consumer purchase behaviour and attempts to fill and act as an originator for future research.

Material and Methods

By investigating a vast amount of academic resources, we tried to depict all available and up-to-day research on neuropsychological, neurophysiological, cognitive, emotional and behavioural perspective to perform a lengthy review and analysis of a large number of studies from selective international journals on issues relating to pricing strategies and consumer behaviour. We originated a predetermined research on numerous research platforms and journals (Advances in Consumer Research, Applied Cognitive Psychology, European Journal of Marketing, International Journal of Psychophysiology, Journal of Advertising, Journal of Consumer Psychology, Journal of Consumer Research, Journal of Marketing, Journal of Marketing Research, Marketing Science, Psychology & Marketing and Science among others).

Our predetermined research was initiated on specific keywords such as neuropricing, neuromarketing, emotions, consumer behaviour, EEG, bias etc to analyse the effectiveness of neuropricing strategies, precisely price endings (0, 5- and 9-endings), fair price, price cut formats (discounts), conspicuous pricing, free offers and dynamic pricing, on human purchase decision making and provided valuable information in order to create and apply more effective price strategies. The outcome generated more than 9.000.000 academic research articles, of which we read and evaluated approximately 500 through a period of 6 months, selecting those ones in compliance to our research.

Results

Price endings

The literature concerning price endings documents that prices are likely to end with 0 (round prices), 5 or 9 (decimal prices) in the marketplace, with each price ending shaping a different perception to the consumer. For example, Schindler [15] indicated that just-below (i.e. decimal) price endings connote low, decreased or discount prices and round-number (i.e. non-decimal) prices connote that the price is high, recently increased or is the full, "regular" price.

It is argued that a large percentage (30%-65%) of all prices end in 9, i.e. €5.99, €9.99 etc [16]. This is a common tactic amongst retailers and some possible explanations, according to the research, include facts such as:

- Customers believe that a 9-ending price is low and discounted, therefore a good opportunity, in contrast to a 0-ending price, which implies high price and quality.
- Customers round prices down ignoring right-most digits, i.e. €99.99 is perceived as €99.
- Customers truncate prices as they process digits from left to right, i.e. €55 and €43 is perceived as €50 and €40 accordingly. Truncation of odd prices is likely to lead to underestimation of prices, which in turn may lead to an increase in sales.

Bizer & Schindler [17] defined truncation as the tendency of consumers to drop off or pay

less attention to the rightmost two digits. In their study, they showed that consumers think they buy significantly more products priced with 99-endings than with 00-endings, while perceiving a 9-ending price as receiving something back (changes).

Gendall, Holdershaw and Garland [18] stated that odd (decimal) pricing can produce higher than expected demand. They are in accordance with Schindler and Kibarian [19] who supported this view after having conducted an experiment by cooperating with a direct mail retailer of women's clothing where they found that 99-ending prices led to 8% more sales than 00-ending prices.

Other studies investigated price endings to determine the type of consumer more likely to use odd-endings as opposed to round-endings. Harris & Bray [20] examined the effectiveness of odd-endings based on the gender and age of the consumers and found that women are more likely to respond with odd-endings than men, while use of odd-endings decrease marginally with age.

A number of studies further investigated the effect of 9- and 0-endings on the image of products. Naipaul and Parsa [21] found that high-end restaurants prefer 0-ending prices in their menus as opposed to 9-ending prices used by mid-level and low-end restaurants. Stiving [22] collected prices from 12 department stores for 30 product categories. The study reported that higher-end stores were more likely to use round prices than lower-priced stores. Moreover, higher quality and higher priced products within a product category tended to be priced with round numbers. Schindler and Kibarian [23] reported that products with 99-ending prices were perceived as having lower prices and lower quality compared with the same products with 0-ending prices.

Schindler [15] further suggested that it might be possible to use price endings to communicate a "fun" image. For example, the repeated use of a very unusual ending such as 71 might suggest certain playfulness on the part of retailer. Or, a leaflet from a charitable trust which talks about its ambitious goals for 1989, and then asks for a contribution of $19.89 may communicate a high-spiritedness that many consumers could find attractive.

Price fairness

Another important issue is the concept of price fairness. According to Xia, Monroe and Cox [24] "*The uproar that occurred when an Amazon.com customer discovered that the price of same-title DVDs differed across purchase occasions was a public relations nightmare for the firm*". This example clearly depicts how a price strategy may lead to price unfairness, which might possibly lead to negative implications to the firm, such as loss of customers, negative word-of-mouth etc.

Price cut formats (discounts)

Studying the effectiveness of various price cut formats (discounts), an experiment by Halpern, Blackman and Salzman [25] found that displaying information in a relative format leads to less risky behaviour. They studied the perception of risk associated with six different formats: natural frequencies framed in a positive format (99,991.7 out of 100,000 will not die), percentages (a 0.0083% probability of dying), natural frequencies (8.3 in 100,000 die), ratios (4.15 times greater risk of death), and percentages (415% greater risk of death). Suri, Manchanda and Kohli [26] also showed that a fixed price format elicits more positive emotions than a discounted price format. In this way, we will evaluate the effectiveness between various types of price discount formats, i.e. "was €50, now €40", "- 20%", "- €10" etc.

Conspicuous pricing

Literature on pricing strategies also discusses the issue of conspicuous pricing. These high-end luxury goods are an interesting type of products that have a fascinating behaviour, where a price increase possibly leads to an increase in demand. Marketers when dealing with conspicuous goods, such as cars, jewellery, perfumes, and watches, try to highlight the exclusivity of their products [27]. According to this study, marketers are motivated to maintain a product's exclusivity because they believe that some consumers might find the product less valuable if it becomes widely available. Bagwell and Bernheim [28] and Corneo and Jeanne [29] argue that conspicuous consumption is a consequence of consumers' desire to signal their wealth. For example, some people may buy a Ferrari merely because many others cannot afford such an expensive car. This phenomenon is more commonly known as “Veblen effect”, named after Thorstein Veblen [30], who in his celebrated treatise on the “leisure class”, argued that wealthy individuals often consume highly conspicuous goods and services in order to advertise their wealth, thereby achieving greater social status. Bagwell and Bernheim [28] stated that "Veblen effects" exist when consumers exhibit a willingness to pay a higher price for a functionally equivalent good, in order for individuals to crave status, and that status is enhanced by material displays of wealth.

Power of free

Other researchers have indicated the power of free. They suggest that consumers tend to overreact positively to free offers relative to low prices, thus free offers are associated with more positive effect and draw more attention [31]. For example, Chandran and Morwitz [32] reasoned that free shipping would have a greater impact on the evaluation of an offer than a discount of equal value because a free promotion would distract people from other considerations. A similar example in another study by Shampanier, Mazar and Ariely [33], refers to Amazon.com when it introduced free shipping in some European countries. Yet, the price in France mistakenly was reduced not to zero but to one French franc, a negligible positive price (about 10c). It was noticed that whereas the number of orders increased dramatically in the countries with free shipping, not much change occurred in France. This supports the findings by Chandran and Morwitz [32] and suggests that when trying to use bundling with a cheap good in order to bring up the sales of another good, it might be wise to go all the way down with the cheap good and offer it for free.

Dynamic pricing

Despite the successful and thriving use of dynamic pricing models on the internet, there is a limited literature in this topic. Kannan and Kopalle [34] defined dynamic pricing as a pricing strategy in which prices change either over time, across consumers, or across product/service bundles. It is in this way a variation of the traditional practice of price discrimination (i.e. discounts for children, students, elderly etc).

Garbarino and Lee [35] stated that dynamic pricing allows the firm to capture a larger share of the consumer surplus, thus being inherently good for the profitability of the firm. It should not be considered in any ways as deceiving or harmful to the benefit of consumers. More precisely, Garbarino and Lee [35] suggested that a strong equity pricing norm is common in the United States. If people there feel that all customers should be offered similar prices, they might react strongly regardless of whether they were offered the higher or the lower price. According to Kannan and

Kopalle [34], the pricing of products and services sold over the Internet channel is becoming more dynamic. This is mainly due to the ease and speed of adjusting prices on the Internet, the low cost of changing online prices, the use of price-comparison bots, the efficiency in measuring demand and tracking competitor prices. Examples of extensive use of dynamic pricing strategies include airlines seats and hotel room bookings. Tools of dynamic pricing involve auctions, reverse auctions (sellers compete to obtain business from the buyer by pushing prices downwards), exchange pricing, bundle pricing (the consumer buys a large amount of a single item to take advantage of a quantity discount) etc.

Conclusions

Our study verifies, through social psychological studies, the effect of pricing on consumer decision making. A great deal of empirical evidence is provided that undoubtedly bolsters the idea that pricing does affect the way customers, who appear to be rather irrational, formulate their purchase decisions. On the other hand, we observe a complete lack of academic research on the effect of neuropricing on consumer purchase behaviour.

Neuropricing can be an integral part of a company's marketing efforts, through which we are able to portray cognition on a neuropsychological level, such as assessing customers' implicit behaviour and reactions to price exposure by analyzing their neurophysiological reactions, to better comprehend the structure and function of their nervous system, during purchase decisions. Using neurophysiological measurements such as fMRI, EEG, facial coding and eye tracking among others, we are in a position of getting bias free information about customer real needs and wants, in order to create the most appropriate price strategies.

As a result, we offer some directions for future research by proposing to incorporate these neurophysiological measurements, to assess the effect of neuropricing on consumer behaviour.

All authors declare that they have no conflicts of interest.

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Testamentary capacity of patients with dementia and of the role of law courts in such cases

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Abstract

Aim of present study is to show if the individuals with dementia, in which are presented on one side disturbances of their cognitive operations and from the other side handing-over of their critical faculty can draw up a will. In Private and in Civil Procedural law is in effect a single system of legal (in)capacity, which is supported in beginnings, methods and criteria that exist mainly in the Civil Code. In step with this system, is in effect also a system of charge, which in general lines is founded in the same beginnings, methods and criteria that are in effect in the system of legal (in)capacity. Common element of these two systems is the will of person. The will as constitutive element of each action of right is interwoven with an uneventful composition of mental operations of individual. Any disturbance of these operations influences the will, or this constitutes element of legal act or element of tort. It has been judged by the case law with abundance of decisions(indicatively they are reported certain from these of (EfThes 703/2008,PolPrSer 149/2012,EfDyMak 31/2014,63/2015) that the simple intellectual reduction- as consequence of ageing- it does not cause disability for drawing up a will, because this development it constitutes physiologic phenomenon of life of individual. Only if cognitive impairment exceeding the normal range can be inferred incapacity for drafting the testament. However, it is judged necessary in any case to be done an individualized approach of particular psychopathological picture of testator. Based on this must be found how much the given dementia is able to influence the capacity of patient from drawing up a will. In conclusion, dementia can constitute reason of nullity of will when it is proved that this impedes the free determination of will of testator and limits decisively the general operation of testators will at the time of writing a testament.

Keywords: Dimensia - Law courts - Testamentary capacity

The regulation of Article 1719 of civil code. The individual cases of disability for drawing up a will

According to the above- mentioned article they are forecasted three categories of persons incompetent for drawing up a will.

More specifically:

A) The underage

B) Those who are found in juridicial support with complete deprival of their legal capacity or with explicit deprival of capacity to draw up a will (custodial guardianship)

C) Those who at the time of drawing up their wills do not have conscience of their actions or are found in psychological or mental disorder that limits decisively their function of will.

In the present work we will deal more analytically with the last from the three cases.

Concretely, the causes of lack of conscience can be or physiological or pathological. In first are included the intoxication, the fever delirium, strong emotions, the intense passions, the use of alchoholic drinks or other toxic substances, the deep old age, death throes, the situation of hypnotism. In pathological belong those that are owed in some morbid event such as epilepsy,

hysteria, the edemas of cerebral form, the cerebral congestion, progressive organic dementia that induce permanent and serious disturbance of the function of mind. Only the existence of testators deafness does not involve itself lack of conscience of his/her actions.

In the provision in question it is transitory disability with the significance that it only concerns the particular will that was drawn up under these circumstances.

Lack of conscience of action exists when the testator cannot diagnose the substance, the content but also the consequences of action that he/she attempts because the above-mentioned situations or illnesses. It is not only enough the diagnosis of situations or illnesses that involve lack of conscience but it is required to demonstrate that these caused in the particular case and lack of conscience of action. Lack of conscience of action does not mean that should this be general and complete. It is enough to exclude the free determination of the will of testator with reasonable thoughts. Case of lack of conscience of action exists when the individual cannot diagnose the substance and the content of the will that he/she draws up neither has the faculty to conceive the importance of the individual provisions of the will.

The one that invokes nullity of will for the reason that the testator did not have at the time of drawing up the will conscience of action, bears also the burden of proof of real incidents. In order to be complete the relevant statement should also be named and evaluated the causes that provoke it for example use of narcotic substances before drafting the testator his/her will. The case law confine itself to invoking lack of conscience at the day on which the testament was written.

Transitory disability for drawing up a will exists also when the testator at the time that he/she draws up his/her will is found in psychological or mental disorder that limits decisively the function of his/her will. Is incurious the disability that befalls later as the one that exists in previous time than the writing of the will.

With the law (L.2447/1996) was imported a new term which is the psychological or mental disorder instead of the term lack of use of reason because intellectual illness (it constitutes legal term that it is not used in the medicine, a term, who with difficulty can be accurately determined, because as intellectual illness is not only comprehended the disease of intellect of spirit ,but as generally speaking each mental disorder).

In the concept of psychological or mental disorder falling both genuine psychoses such as manic-depressive psychosis, schizophrenia, insanities, as much organic- mental illnesses, that are owed in pathological alterations of cerebral web or in disturbances of physiology of the brain, such as for example progressive general palsy, multiple sclerosis, epilepsy, senile dementia, dementia from diabetes etc. Consequently are included so much the mental diseases that are not owed in bodily-organic reasons(endogenous psychosis) but also mental disorders that are result of other illnesses or wounds of brain or dysfunctions.(exogenic psychosis).

The applicable provision of article 1719 of the civil code number 3 simply requires in order to be applied psychological or mental disorder that limits decisively the function of will and decrease considerably the objective control of reality. Law does not make discrimination between permanent and transitory illness in the heavy illnesses or in diseases that cannot be cured, but is sufficient if the applicant proves that the testator suffered from this illness at the time of drawing up the will.

If it is disease that is not curable or heavy mental disorder which excludes the existence of luminous breaks (on schizophrenia is excluded the existence of luminous breaks, is enough the proof that the testator is deprived at the season roughly (not therefore precisely the day or even the hour)

of drawing the will, the use of logic. The fact that at the time of writing the will the testator was psychopath or hospitalized in a psychiatric clinic does not mean that he/she lacks the capacity to write a will but will be judged in the particular case how much this illness has influenced his/her crisis.

If however the disease is periodical or transitory it is required once again to prove the mental disorder of the testator at the time of drawing up the will.

Question that needs answering is if in the term mental disorders can be included also the sentimental disturbances of individual as for example a neurotic depression which is so much intense and because of it the individual cannot freely decide for the way of disposal of his/her fortune. The answer in this question is positive based on the grammatical interpretation of provision of article 1719, section a, number 3 of civil code because the legislator for the existence of mental disorder is focused only in the decisive restriction of will of testator from this disturbance.

Further the restriction of will as it was reported above, should be decisive because of psychological or mental disorder. Decisive restriction exists more specifically when the function of will suffers from perturbation in such a great extent that the testator cannot conceive neither the importance nor the consequences of his/her statement. And therefore in order to determine whether the restriction was decisive, because of psychological or mental disorder, must be apprised all the circumstances both objective and subjective.

Is not excluded by the law the coexistence in the testator both situations of disability that are forecasted in the article 1719 number 3 of civil code.

Special report must be done to the ability or otherwise of senile age persons that suffer from mental disorder (senile dementia or progressive organic dementia). The simple intellectual reduction- as consequence of ageing- it does not cause disability for drawing up a will, because this development it constitutes physiologic phenomenon of life of individual. Only if cognitive impairment exceeding the normal range can be inferred incapacity for drafting the testament.Concretely the testator who suffers from senile dementia can conceive sufficiently what precisely makes when draws up a will but because the lack of conscience and mental disorder, because of his/her disease cannot allocate free will as a mental healthy person, and because of this cannot have the ability of resistance in any form of submission it emanates from other. The weakness of regular choice of springs and specifically the sentimental and impetuous tendencies for the configuration of will is the decisive criterion in order to be realised the disability of testator. However, it is judged necessary in any case to be done an individualized approach of particular psychopathological picture of testator. Based on this must be found how much the given dementia is able to influence the capacity of patient from drawing up a will. In conclusion, dementia can constitute reason of nullity of will when it is proved that this impedes the free determination of will of testator and limits decisively the general operation of testators will at the time of writing a testament.(Psoyni 2014; Koytsoyradis et al.,2008; Triantos, 2015; Karakostas, 2008; Mpalis, 1965)

Case law of courts

Then we will deal analytically with somebodies from the affairs that occupied the courts, which concerned the nullity of drawing up a will because application of article 1719§3 of civil code. Specifically, it has been judged by the case law with abundance of decisions (AP 1145/1999, Ef Ath

143/2000, EfLar 89/2001,AP 1680/2002,AP 1363/2004, AP 1612/2005, AP 1358/2006, Ef Ath 7808/2007, EfThes 703/2008,PolPrSer 149/2012,EfDytMak 31/2014, EfDytMak 63/2015), in some cases that the will is null because of senile dementia of testator at the time of writing the will and in other cases that dementia does not exist and therefore there can be no reason for invalidity of the will.

Also exist other decisions in which the courts cancel the will AP 374/1999, PolPrPeir 3926/2002, EfAth 3192/2003, EfAth 885/2003, because application of article 1719§3 of the civil code, on other however reasons from those that invoked the courts of previous paragraph, and concrete in one from these cases the court judged that when the testator wrote his/her public will was in complete lack of conscience because death troes. In the remainder cases previously the court judged that the mental disorder of testator (for example schizophrenia) influenced his/her mental situation and previously it judged the court that despite the existence of mental illness, the time interval of training of controversial will, the testator presented smooth behavior, apprising of course the court and the remainder activities of testator in the various sectors of his/her life.

The court in this decision (AP1145/1999) contained the following admissions and explanations. The testator at the time of drawing up her self-composed will and concretely in 20/5/1977 was 83 years and suffered from senile dementia, consequence of which was that she did not have use of reason, and in particular was excluded from her the free determination of her will with reasonable calculations. Her symptoms began to present three years before the writing of her will and with the byway of time the situation worsened, so much that many times she presented inconsistency in her thoughts and proceeded in actions which she did not conceive the content of them and the consequences.

More specifically before the drawing up of the controversial will she hospitalized in two regular time intervals, the first time (from 19/3/1974 until 23/4/1974) in clinic Nik.L. because of senile psychosis with elements of mental handing-over and the second time (from 25/6/1976 until 20/2/1977) in the neuropsychiatric clinic Ag.Servant because of senile dementia with stimulant seizures.

The illness of senile dementia was permanent and lasting and not temporary or periodic nature with exclusion of luminous breaks, has developed and expressed completely at the last interval of her hospitalization, as well at the time of drawing up her will, thus caused and to exist at that time, because of senile dementia inability weighting logic and free determination of her will.

According to the second decision that we will examine analytically (AP 1680/2002), the court judged that based the real incidents does not enjoy application the article 1719§3 of the civil code, because invocation of senile dementia of testator. In particular based on the real incidents the testator A.A. (given birth in 1910, according to the passport and her statement of death) she died in Athens in 26/3/1991, leaving two public wills (16248/1982 and 1798/1987), that were drawn up in front of notaries A.P and E.R. and were published legally. With them she left her entire fortune in an under constitution institution with the name “Institution Beneficial to the public N. and N.A” aiming at the issuing of scholarships.

In the particular testaments were determined without further conditions and the persons that would fix the scholars of institution. In the particular persons were included inter alia the applicants, the second defendant, the descendants of D.S (father of the applicants) and descendants of defendants.

Because of her big fortune she used also other individuals for the management of her affairs, between these persons was also the mother of first defendant E.M. as well as the cousin of hers E.S. who was mother of claimants.

In the first defendant M.P., which the testator knew her from childhood, she had assigned the transaction of her financial affairs, rendering her procurator with specific proxies, while in second defendant she had assigned again with proxy, the management of those assets which were determined from the particular proxy.

On April 10, 1999 A.A. called in the hotel she was staying the known to her notary E.R. and drew up two notarial actions. With the first of which she recalled her previous public will (number 2138/87) and with the second notarial action, that constituted her new public will, installed her general heirs at ½ from indivisible each one of the defendants in all her mobile and motionless fortune.

The court accepted based on the real incidents that at the controversial interval the two notarial actions were drawn up that the testator did not suffer from senile dementia and is not placed consequently question of application of article 1719§3 of civil code as claim the applicants. Moreover despite the fact that the testator was 79 years at the time of drawing up the two notarial actions was in mental clarity. Finally the court judged that the testator until her death had intellectual lucidity, and because of it she could take care to her personal situation but also to manage her fortune. Her intellectual lucidity is also proved by the fact that she did not have aberrations or voids in her memory, did not resort never in neurologist or other psychiatrist, neither took other medicines or tranquillizers, despite only these pills for the heart. Finally the court accepted that the change in her behavior as for the establishment of institution beneficial to the public was justified, not due to clouding of intellect and lack of conscience but because her concern that she also had confined in her lawyer I.K. since the begging of 1988, saying that “those who manage the institutions eat her money and must be found a way to take her money someone that will be interested for her”.

All authors declare that they have no conflicts of interest

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Primary care services provided to persons with dementia under the "Help at Home" scheme of the Municipality of Chios

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Abstract

The "Help at home" scheme is the only nationwide state structure of residential care to elderly and disabled people since 1998. The primary care services provided vary in frequency depending on the severity of the health problems and socioeconomic conditions of each patient. Chios has 7 structures extending from the city center up to distant villages. In addition, the island does not provide any organized care structure for dementia patients or their caregivers. This study is based on whether people with dementia receive increased frequency of services compared to other categories of diseases given the total discount functionality of dementia and the burden of their family environment. For this purpose, analytical transcripts of weekly and monthly log of visits of personnel programs have been used, as well as medical and social histories of the patients. Compared to other disease categories an increase in the frequency of specific services has been observed, such as interaction with organizations and family, social support to people with dementia, family support and household cleaning. Additionally, a significant differentiation according to the geographical distribution has been notified, which is related to three factors. First, the proximity of the place of residence of the relatives of the patients becomes a major parameter because the care of the old parents has an important role by the social standards of the island. More precisely, the naval character of Chios constitutes the implicit and moral obligation of children to take care of elderly parents. Secondly, accessibility to secondary health care units is restricted in the most distant areas. Third, the private provision of services in distant areas is too expensive and so the provision of free care from the scheme facilitates the financial burden of the patients. Finally, the lack of skilled professionals specialized in dementia on the island increases the need for local specific structures.

Keywords: Dementia - Patients - Carers - Provided services - Help at Home.

Introduction

Demographic and population aging in developed and developing countries have as a result the increase in the incidence of diseases caused by the mental and physical decline that comes with aging. Among these, dementia is considered as one of the most complex and difficult to treat disease worldwide. [1,2]. Alzheimer's Disease International (ADI) estimates that there are currently about 47 million people with dementia in the world, a figure that is expected to double or triple by 2050 (www.alz.co.uk; www.alzheimers.net). In the European Union, respectively, there are 6.4 million people with dementia (http://ec.europa.eu;) and in Greece, about 200,000 patients. This numerical increase, combined with the changing economic-social conditions and increased recognition of dementia as a disease, is expected to exacerbate the demand for services and therefore the cost of

care will increase dramatically [3].

In the face of this need for care, “Help at Home” provides free residential primary care to elderly patients and people with special needs. The main goal of the project is to improve the quality of life of the people who need support services, nursing services or residential care, in order for them to remain in their familiar physical and social environment, to preserve their family cohesion, to avoid institutional care and social exclusion, as well as to ensure a decent standard of living (www.eetaa.gr). Equally important is the emotional and psychological empowerment of the caregivers, which is offered through the services of the program.

Description of the population

The total number of people served by the 7 program structures that operate on the island is 522. Regarding the gender of the population, most patients are women (357, 69%) with a remarkable increase of three times compared to men in the age groups over 71 years. Regarding age, 2/3 of the population are in the category of over 71 years, with a significant concentration of over half of the population in the age category over 78. The 7 program structures meet the needs of the 64 villages and the city center of Chios. About half of population of the research (48%) reside in remote areas of the island, while 38% of the population live far from the center and away from the secondary care unit of the island (General Hospital of Chios "Skylitseio"), therefore their medical care is limited.

Based on the health records and medication of people who receive the care services, it is concluded that 1/5 suffers from cardiovascular diseases, followed by mobility problems, psychiatric disorders, diabetes and, at 11%, dementia, mostly senile.

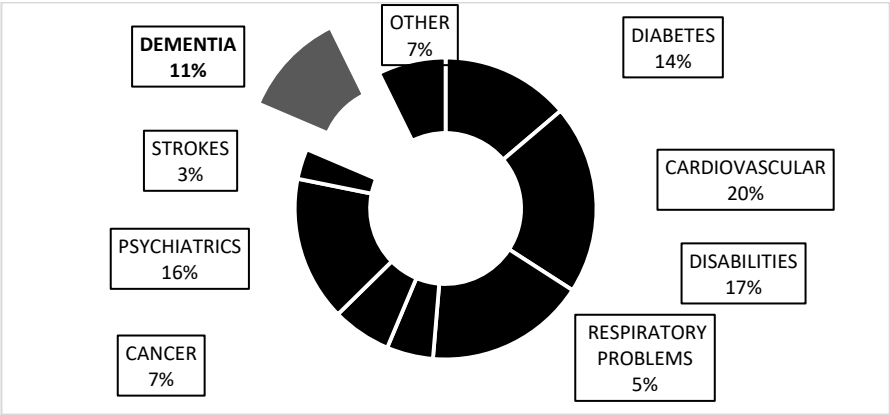

Figure 1. Classification of beneficiaries based on their diseases

It should be noted that the 11% of people with dementia is estimated to be lower than the actual figure because the memory problems and the deterioration of the functionality of patients in the early and middle stages of the disease are not easily recognized [4-7] as primary disease symptoms. Early diagnosis is further inhibited [8] by the failure to identify the severity of symptoms, as they are considered a normal consequence of aging, symptoms of another medical condition, denial or fear. Also, in Greece the time from the first observation of symptoms until the diagnosis is 13 months.

Help at Home services

The program is staffed by health professionals such as psychologists, sociologists, social workers, nurses, family helpers and physiotherapists, who provide a range of free primary care and preventive services (in cooperation with other organizations) on the island. Specifically, 11 types of services per month are provided to the people registered in the program, as shown in Figure 2.

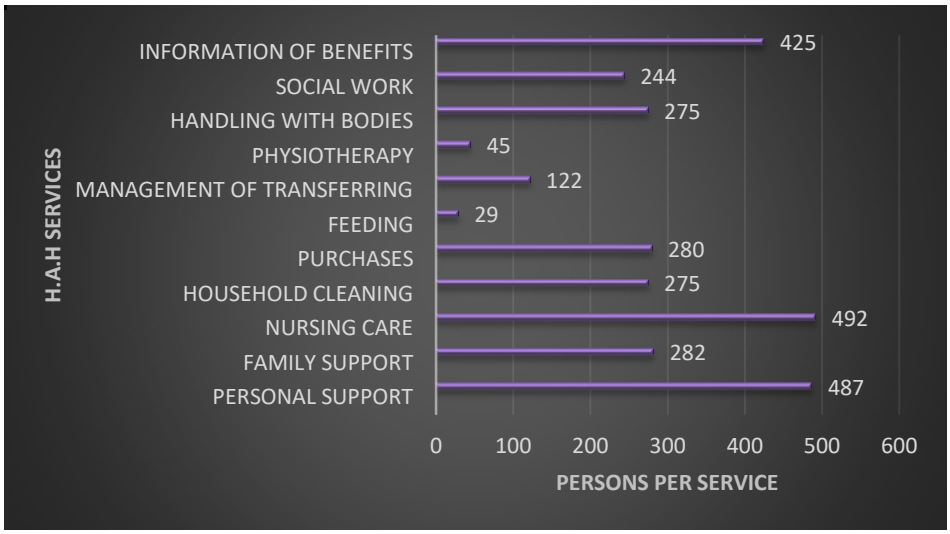

Figure 2. Types of Help at Home services per month

The plan of the services is formed based on the needs of the people served. The lack of medical and nursing staff in the remote regions of the island, the long distances from the hospital and the high cost of hospital and medical actions by private entities require the presence of "Help at Home" close to people, with nursing care service being the top priority, followed, in terms of frequency, by the individual social support and information on benefits provided to the person in need. It has been observed that the indirect benefit of carers of the elderly in Chios, helps them both in terms of the financial burden (about 80-200 euros per person, on a monthly basis), and in terms of their physical and emotional discharge and empowerment [9,10].

Case

Given the gradual decline in the functionality of patients with dementia and the complete disorganization of their personality, the case of this study is based on the fact that people with dementia have an increased use of certain services provided by the scheme, compared to the other 10 disease categories.

Methodology

To test the case we used the statistics with data about the beneficiaries from the last half of 2016, for 7 structures operating on the island, personal and family social history, health records of the beneficiaries, but also weekly and monthly tabs with the visits of the scheme employees per structure, involving 11 types of services. These are the same ones which are sent on a monthly basis to the administrative body of the Help at Home scheme, the Hellenic Agency for Local Development and Local Government. Finally, for 59 people with dementia, interviews were conducted with the

heads of each structure in order to collect and analyze more data.

Description of the study sample

59 individuals with dementia were studied, the vast majority of which (95%) are women over 65 years of age. A large percentage of the sample (65%) reside in remote areas of the island. 3 out 4 patients with dementia are lonely people due to widowhood or celibacy, which makes the need for caregivers imperative (see Table 1).

Table 1. *Descriptive data of patients with dementia in the Help at Home scheme*

Gender		Residence		Age		Family Status	
Men	3	Countryside	33	<65		Married	15
Women	56	City	26	>65		Non married	3
						Widow	43

Regarding the care of patients with dementia, a large percentage (78%) of the patients of the sample are taken care by companions, children and relatives. In Greece, 89% of Alzheimer's disease patients are cared for at home and 77% of the caregivers are women [4]. The high requirements for the care of people with dementia, maximizes the so-called "burden" of carers, as it has a negative impact on their physical and mental health, drastically limits their free time and shakes their social, professional and economic security [2, 11, 12].

By studying the traditional family model which prevails by the social standards of Chios [13-15] - where, because of the naval tradition, the obligation of relatives to care for their elderly family is considered implicit - the findings on the sample were verified. On the other hand, only a small percentage chooses to hire caregivers. Only 8% of the caregivers needs auxiliary help for their patient care.

Observing the distribution of services offered to people with dementia, we notice that, while the frequency is constant (1 time per week) in the city and nearby areas, at remote regions, 18 of 32 patients with dementia increase the frequency of visits to twice a week. People living in remote areas seem to have limited financial resources and they live far from their close relatives, in villages where the population is mostly senior citizens. Therefore, 1/3 of the sample increases the weekly “Help at Home” services by one more, as shown by the weekly reports of the scheme.

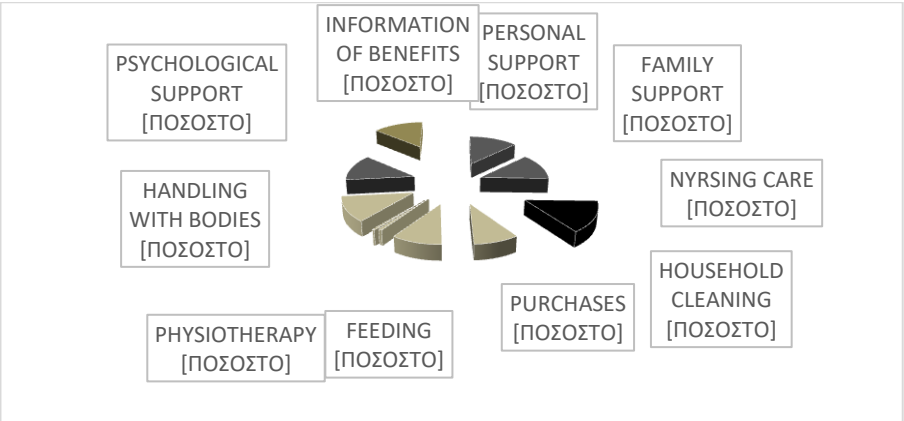

Figure 3. Help at home services for people with dementia

Equations

To test the working hypothesis we compared the ratio

$$\frac{Numberofpatientsperdisease}{Totalnumberofpatients} \quad (1)$$

and the ratio

$$\frac{Numberofpatientsperdisease—use\ of\ each\ service}{Totalnumberofpatients—use\ of this service} \quad (2)$$

For example, 59 patients with dementia of a total of 522 patients make up 11.30% **(1)**. Looking at the individual social support, it is used by 51 patients with dementia (i.e. 86,44% of the sample) of a total of 445 patients of all categories who benefit from the specific service, accounting for 11.46% of all the persons who receive individual support **(2)**. And, since in the period in question there is no change in the number of both patients with dementia and other categories, each percentage change in the use of each service, entails a corresponding change in its weekly frequency.

Comparison of the services provided to patients with dementia with the rest patients categories

Dementia is the fifth more common disease in the “Help at Home” population, with cardiovascular diseases being first. The number of supported people for each disease affects each service provided. However, dementia is 4th in average of the total use of services provided by the scheme. In particular, examining separately each service provided and associating it with the disease categories, we get the following results.

Personal social / psychological support and information about the benefits of the eligible patients

Regarding the personal social support, patients with dementia are 11,30% of the total population and a corresponding use of the service should be expected. However, 11.46% receive this service, showing a marginal increase in the weekly provision per person (0.025). The frequency of psychological support (1 time per week) to people with dementia also doesn't change compared to other categories.

93% of the sample receive a weekly update on matters that concern them. The classification

of people with dementia in the third place, regarding the use of this service over other patients, demonstrates the importance of information and training of the caregivers, which, based on the existing literature, is often characterized incomplete (www.alzheimerathens.gr).

Family support

The involvement of the immediate family to the disease is confirmed not only in literature, but also by our research results [5]. The greatest need is focused on the psychological support of the caregivers and mental strength training for people up to the second stage of the disease [10].

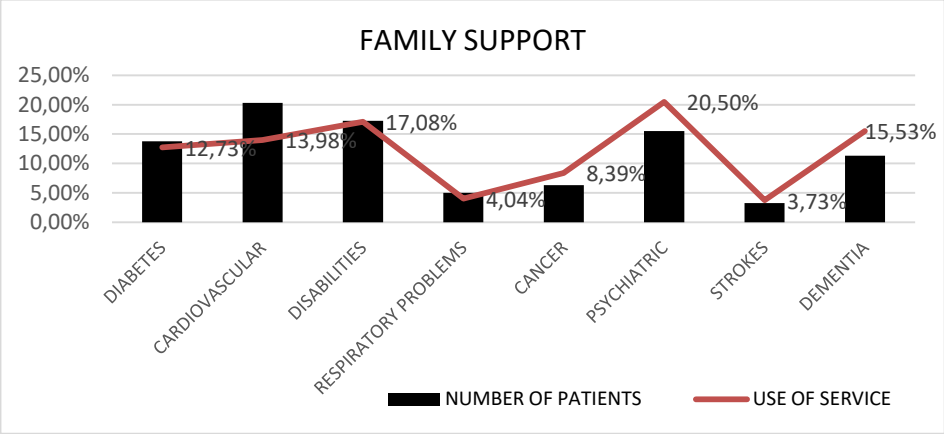

Figure 4. Family support to people with dementia in compared to other diseases

Compared with other diseases, the second - below psychiatric disorders - greatest percentage increase in family support is noted for people who suffer from dementia. And while the service users are reduced by 9 persons, the use percentage is increased, and, consequently, the frequency of family support, changing the weekly use about 1.5-2 times.

Nursing care and physiotherapeutic intervention

It is noteworthy that while huge sums are considered for the nursing care of patients with dementia, and the importance of residential nursing care for the course of dementia is emphasized, (Sloaneetal, 2001; www.alzheimers.net), “Help at Home” contributes greatly to reducing both family and public health costs, but also slowing the physical symptoms of the disease.

11. 59% of the people with dementia use this service while there is consistency in the frequency of the weekly nursing care.

Only 2 in 59 people receive physiotherapeutic intervention of a total of 42 persons of the population. This is explained by the fact that, although the scheme includes physical therapists, they are not enough for all “Help at Home” structures and the demand is reduced.

Household cleaning, buying basic necessities and food / nutrition

62.71% of people with dementia receive household cleaning services.Compared with other diseases dementia comes second, thus increasing the provision of the service at two times a week. Specifically, this service is requested by lonely people, mostly without children, low income pensioners or residents of remote areas.

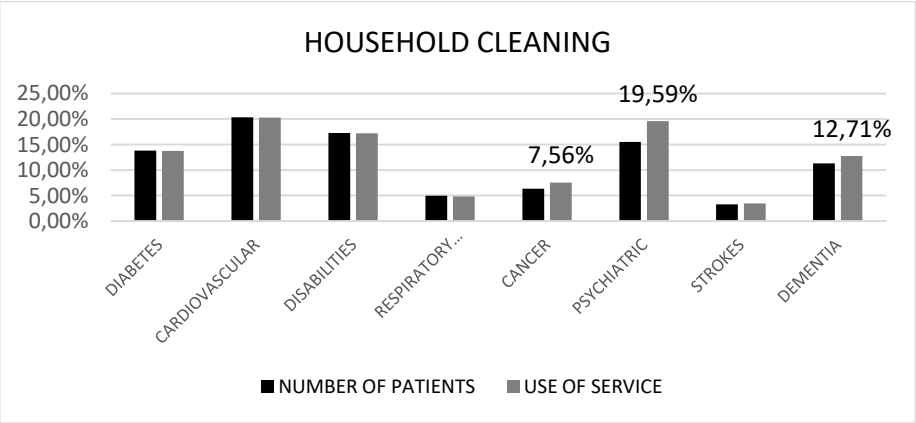

Figure 5. Household cleaning for people with dementia compared to other diseases

Only 3 in 59 people with dementia receive supportive care in preparing food and feeding. Compared to with other diseases, dementia comes third in the use of the service, as only 19 people of the total population benefit weekly bringing this service to three times a week!

Handling with bodies

Contact with public services, health committees, social organizations, associations, local communities, doctors, social security organizations etc. is made through "Help at Home" by all specialties. 83% of the sample requests contact with various organizations, changing the service provided by 0.5-1 weekly. It is the third disease with high rates of use of this service.

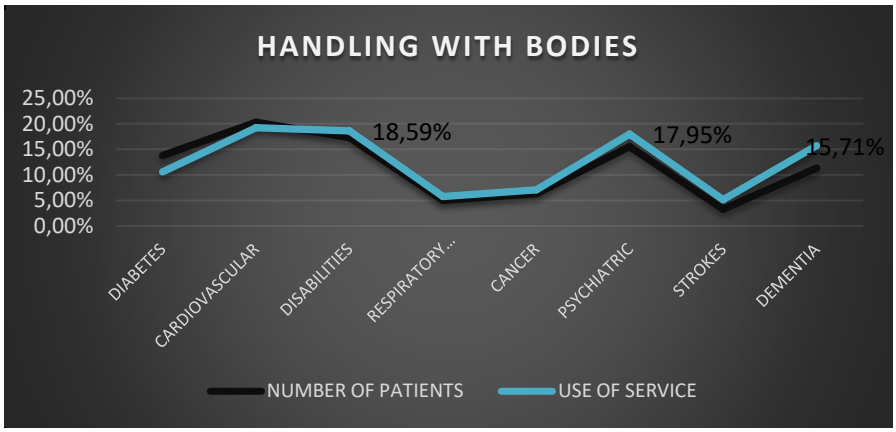

Figure 6. Handling with bodies for people with dementia, compared to other diseases

Management of transferring

As expected, half of the patients with dementia receive assistance with travel by the staff of the scheme. Compared with other diseases it is estimated that 3-4 times weekly the above persons are served, because of the gradual deterioration of their functionality due to the stages of dementia.

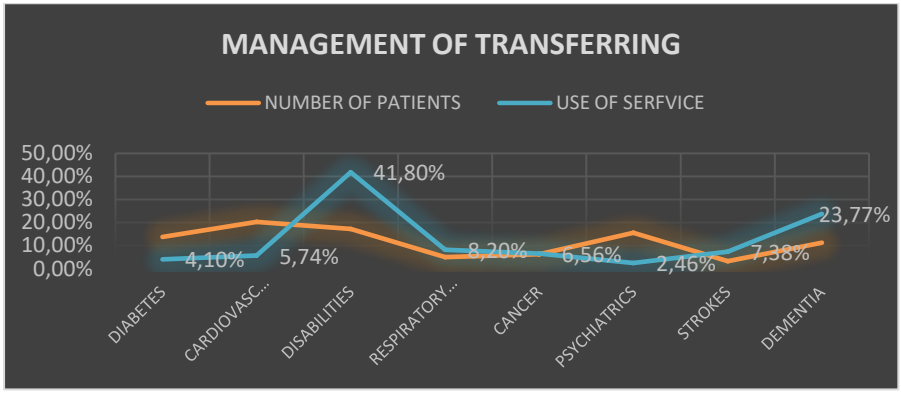

Figure 7. Management of transferring for people with dementia, compared to other diseases

Conclusions

The study of the results of this research demonstrates the increased care needs of people with dementia compared with other patients of the scheme who suffer from equally serious diseases. It is found that the kinds of services that patients with dementia use at an increased frequency confirm the necessity for daily care and education for patients and caregivers. If one considers that for 6 of the 11 services of the "Help at Home" scheme (family support, contact with organizations, buying basic necessities, household cleaning, feeding and help with transferring) the weekly frequency of visits increases from 1.5 to 3 times, the necessity of the scheme for people with dementia becomes obvious. Furthermore the naval tradition of the island and the social norms regarding the care of elderly patients with dementia by the family environment, create an urgent need for training and psychological support to carers. The coverage of the ever increasing medical, social and psychological needs of patients with dementia in their familiar family environment is a challenge in terms of state care with the goal to ensure the autonomy of patients with dementia and their families, and to avoid social exclusion and institutionalization of these patients. The awareness and the formation of an organized interconnection framework between policies, mental health professionals, researchers, carers and people with dementia emerges as the modern realistic need to optimize the tactics for effective management of the symptoms of dementia.

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All authors declare that they have no conflicts of interest

Useful Internet addresses:

World Alzheimer Report 2016, Improving healthcare for people living with dementia coverage, Quality and costs now and in the future ADI (www.alz.co.uk)

www.alzheimers.net/resources/alzheimers-statistics

http://ec.europa.eu

www.alzheimerathens.gr

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Use it more and keep it alive: a Longitudinal Randomized Controlled Trial in people with Mild Cognitive Impairment

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Abstract

Objective: To assess the effectiveness of two years versus one year of cognitive training in people with amnesic and multi-domain MCI. Methods: One hundred and six MCI patients were randomly assigned in two groups, one experimental (n=74) and one control (n=32). Seventy-four attended a systematic one year cognitive training program, while 41 of them attended the same cognitive training program for one more year. The control group (n=32) did not take part in any kind of cognitive or pharmacological therapy. 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 ($p=0.005$) memory, executive function ($p \leq 0.008$), daily activities ($p \leq 0.025$), general cognitive ($p=0.020$) and functional performance ($p=0.003$). At the two-year follow-up, the group with two years of training (N=41) had better performance than controls in verbal ($p \leq 0.005$) and visual ($p=0.001$) memory, executive function ($p \leq 0.012$), daily activities ($p \leq 0.004$), and general cognitive and functional performance ($p=0.000$). The group with two years of training had better performance than the group with one year of training (n=33) in verbal ($p=0.007$) and visual ($p=0.007$) memory, executive function ($p \leq 0.009$), daily activities ($p=0.009$), and general functional performance ($p=0.000$). The group with one year of training had better performance than controls, in executive function ($p \leq 0.013$), general cognitive ($p=0.016$) and general functional performance ($p=0.009$). Conclusion: Two years of cognitive training are more beneficial to people with MCI than one year of training or no training at all.

Key words: Cognitive training; longitudinal intervention; Mild Cognitive Impairment

Introduction

The continuously growing elderly population is one of the reasons of the increased prevalence of age-related disorders, such as Mild Cognitive Impairment (MCI) [1]. MCI refers to a transitional zone between normal cognitive function and clinically probable Alzheimer's disease (AD) [2]. According to Petersen, MCI may entail symptoms not only in memory but also in other cognitive domains [1, 3].
People with MCI can benefit from brain plasticity mechanisms after being exposed to performance optimizing conditions, such as cognitive training [4, 5]. The aging brain can indeed learn and relearn

due to brain plasticity [6, 7]. Brain plasticity activation requires a change in cognitive strategies and new learning. Thus, through repeated intense and specific cognitive practice the elderly may train and preserve their cognitive capacities.

Studies show that cognitive training benefits the specific cognitive functions that are trained [8, 9]. Moreover, Belleville's review [10] has shown that cognitive training may optimize the cognitive functioning of people with MCI, while data from the ACTIVE study have shown that cognitive training improves cognitive functioning in well-functioning older adults, and that this improvement lasts up to 10 years follow up [11]. Therefore, taking into account the dubious data on the safety and efficacy of cholinesterase inhibitors (ChEIs) in people with MCI [12] and the retained brain plasticity in aging [4, 5, 13] it is important to study the benefit of longitudinal cognitive training on cognitive and functional performance.

This study was designed to follow up people with MCI of amnestic and multiple domains subtype (aMCImd) for two years. The aMCImd subtype was chosen, because it is the most frequent type of MCI in the general population [14], it is closer to AD and it is in greater risk to develop dementia in the future [15]. Our hypothesis was whether two years of cognitive training would have better results in cognitive and functional performance of people with aMCImd than one year of training, or no training at all.

Methods

Participants

The participants were visitors of the Day Care Center of Alzheimer Hellas. They were diagnosed with aMCImd according to the 2004 Petersen criteria [3] by specialized health professionals. A diagnosis of aMCImd was made following neurological examination, neuropsychological and neuropsychiatric assessment, medical/social history, neuroimaging and blood tests.

The initial study sample (n=192) was recruited from September 2012 to September 2014. Thirty-five people were diagnosed with dementia and they were excluded from the study while 6 people were excluded because of uncontrolled medical problems. Thus, 151 people were randomized by using an algorithm in two groups (80 in experimental group and 71 in control group). Out of the 80 people of the experimental group, three were excluded because they had missed more than ten sessions during the first year of training, while three patients withdrew the study because they encountered severe medical problems. Thirty-three people stopped the training at the end of the first year, but they agreed to return for a follow-up one year later. These people did not differ in age, sex, education, cognitive and functional performance in comparison to the rest of the participants who completed the two years training. Fifteen people out of the control group were lost to follow up, while 18 people withdrew the study. Three people were excluded because of severe medical problems.

Finally, 106 people participated in the study (Figure 1). The experimental group comprised 74 aMCImd patients with a mean 27.81 (*SD*=1.46) Mini-Mental State Examination (MMSE) score, while the control group comprised 32 people with aMCImd with a mean MMSE 27.37 (*SD*=1.73) score. According to the Mann-Whitney test, there were no statistically significant differences between the two groups in age (p=0.060), education (p=0.054) or gender (Pearson's Chi Square p=0.477) at baseline, neither in cognitive and functional performance. Participant's baseline characteristics and their cognitive and functional performance are presented in Table 1.

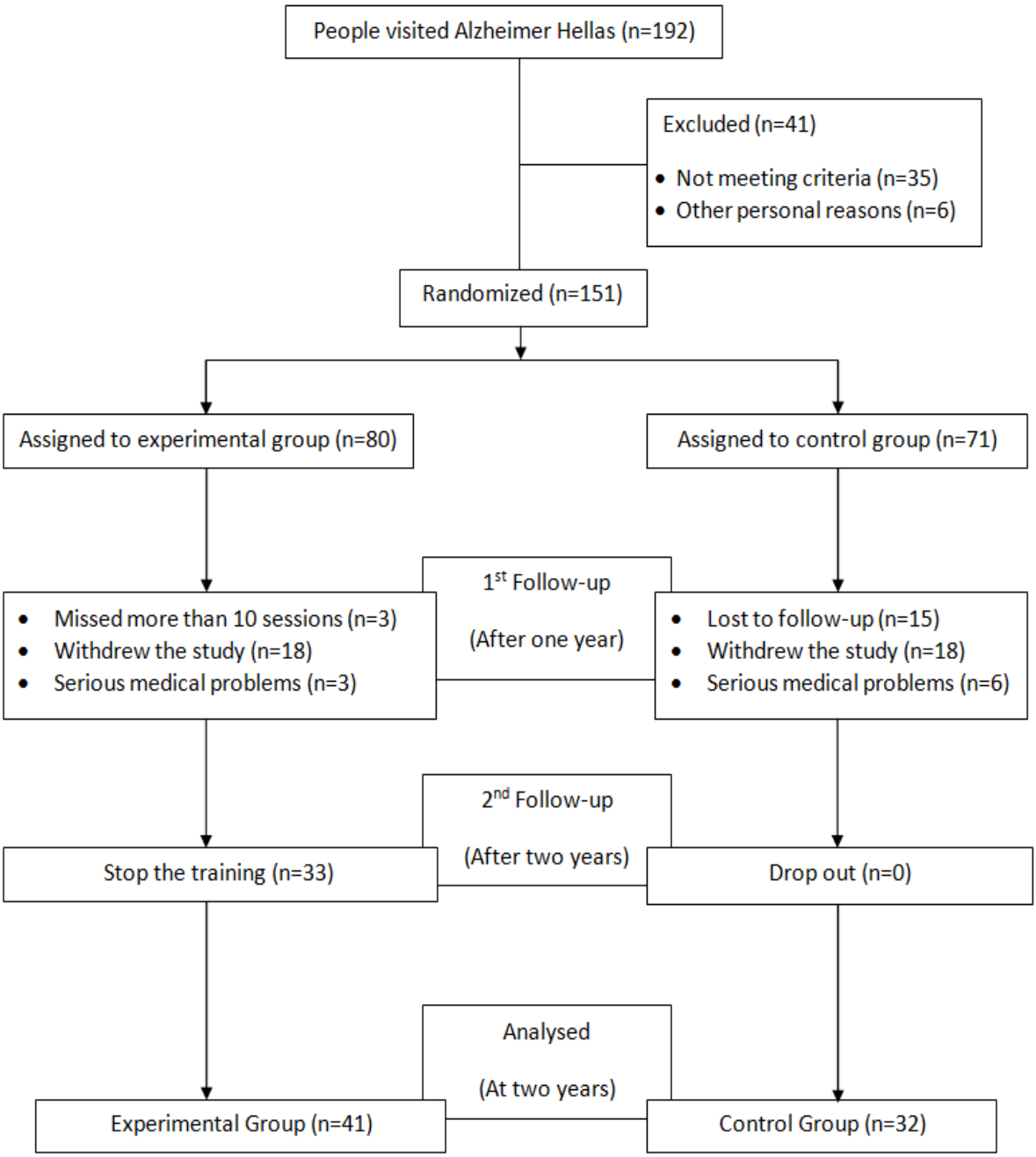

Figure 1. Flow of initial sample

Table 1: Participants baseline characteristics (Mann-Whitney and Pearson's Chi Square exact test)

Characteristics Cognitive/Functional Performance *M (SD)	Control Group (n=32)	Experimental Group (n=74)	p
Age	72.71 (6.25)	70.51 (5.92)	0.060
Gender (Male/Female) Pearson's Chi Square test	5/27	16/58	0.477
Education	10.06 (3.70)	11.12 (4.08)	0.054
General cognitive function (Total MMSE)	27.37 (1.73)	27.81 (1.46)	0.102
General Functional Performance (Total FUCAS)	44.00 (2.12)	44.00 (1.96)	0.483
VERBAL MEMORY			
Digit Span (RAVLT)	4.31 (1.69)	4.78 (1.98)	0.111
Learning ability (RAVLT)	9.87 (2.25)	10.18 (2.47)	0.306
Delayed recall (RAVLT)	6.87 (3.32)	6.95 (3.24)	0.475
VISUAL MEMORY			
Complex figure delayed recall (ROCFT)	10.17 (5.58)	12.07 (5.31)	0.051
EXECUTIVE FUNCTION			
Planning (FUCAS)	6.06 (.24)	6.14 (.42)	0.225
Prospective memory (FUCAS)	5.56 (.80)	6.56 (.77)	0.486
Accuracy of steps (FUCAS)	6.34 (.48)	6.31 (.52)	0.334
Sequence of steps (FUCAS)	6.06 (.24)	6.02 (.16)	0.355
Goal maintenance (FUCAS)	6.90 (.96)	6.87 (.52)	0.472
DAILY ACTIVITIES			
Telephone communication (FUCAS)	8.00 (1.24)	7.93 (1.23)	0.378
Shopping (FUCAS)	7.34 (.82)	7.31 (.75)	0.454
Medication (FUCAS)	7.31 (.73)	7.31 (.72)	0.593

*M (SD) = Mean (Standard Deviation), p = Significant difference of performance between the two groups

Inclusion and exclusion criteria

The inclusion criteria were:

(1) ≥ 60 years of age
(2) Subjective cognitive complaints
(3) A diagnosis of aMCImd in agreement with Petersen's [3] criteria
(4) Spared language skills, e.g. speech comprehension and production. Language skills were assessed during the interview performed for the social-medical history.

The exclusion criteria were:

(1) Diagnosis of dementia according to NINCDS-ADRDA criteria [16]
(2) Severe psychotic traits, untreated depression (Geriatric Depression Scale-GDS≥6), untreated anxiety (Beck Anxiety Inventory -BAI≥7), agitation or behavioral problems according to the Neuropsychiatric Inventory (NPI) that might prevent successful participation in the program

(3) Other neurological disorders such as stroke or ischemic lesions
(4) Use of antipsychotics
(5) Pharmacological treatment with ChEIs
(6) Sensory deficits e.g. in visual acuity or hearing, assessed by a neurologist

The participants signed an informed consent and were aware that they could withdraw their consent at any time without their statutory rights or medical care being affected.

Study Design

Seventy-four people with aMCImd attended a cognitive program during the first year at the Day Care Center of Alzheimer Hellas, at the same time in the morning. Cognitive training included specific cognitive abilities tasks. The primary aim was to enhance cognitive parameters of executive functions and specifically problem solving abilities, e.g. planning, prospective memory, accuracy, sequence and goal maintenance. The secondary aim was to generalize new learning in other cognitive domains such as memory. The intervention adopted a multi-component approach including a range of 3 cognitive programs. All of them had the same cognitive structure, but a different means of training e.g. paper and pencil tasks, motion instructions, computer software, reality orientation in current events, and musical stimuli tasks. The tasks were ecologically valid as they were derived from activities of daily living and they were not similar to the tasks included in the neuropsychological tests.

The cognitive training included 34 weekly sessions, each of which and each one lasted 4 ½ hours. Six trainees attended 3 cognitive programs in each session under the guidance of 3 trained psychologists who were engaged to apply the same cognitive program during the whole study.

Forty-one people continued the training for one more year and attended 34 weekly sessions, while thirty-three trainees withdrew from the training in the second year. They came back one year later for the second follow-up. The control group did not take part in any kind of cognitive or pharmacological therapy. Both the study and the training programs were approved by the Scientific and Ethics Committee of Alzheimer Hellas.

The effectiveness of the intervention was examined by neuropsychological assessments, performed at baseline, one and two years later.

Neuropsychological assessment

The neuropsychological assessment included a battery of psychometric tests assessing visual and verbal memory, cognitive parameters of executive function e.g problem solving abilities, daily life activities, and general cognitive function [17] (Table 2).

The neuropsychological assessments were performed by the same psychologist who was not aware of the participants' assignment and the purpose of the study. Practice effects in test performance due to familiarity did not occur because different test versions were used, wherever available.

Table 2: Neuropsychological battery

Cognitive Ability	Tests	Measures
General cognitive function	Mini Mental State Examination (MMSE) (Folstein 1975; Fountoulakis 2000)	Total raw score‡
General Functional Performance	Functional Cognitive Assessment Scale (FUCAS) (Kounti 2006)	Total raw score†
Verbal learning	Rey Auditory Verbal Learning test (RAVLT) (Rey 1958)	Learning ability‡ Delayed recall ‡
Visual memory	Rey Osterrieth Complex Figure Test (ROCFT) (Rey 1941)	Complex figure delayed recall‡ Planning†
Executive function	Functional Cognitive Assessment Scale (FUCAS) (Kounti 2006)	Prospective memory † Accuracy of steps† Sequence of steps† Goal maintenance†
Daily activities	Functional Cognitive Assessment Scale (FUCAS) (Kounti 2006)	Medication† Shopping† Telephone communication†

Statistical analysis

For the statistical analysis the SPSS 20.0 software was used. According to the Kolmogorov Smirnov test the sample's performance did not follow the normal distribution. Therefore, non-parametric tests were used, such as Mann-Whitney test for two independent samples for between-group differences at baseline, 1st and 2nd follow-up. We used a Chi square test in order to detect possible differences in gender and a Wilcoxon test for two related samples in order to examine within group differences between the first and the third assessment. Furthermore, a Chi square test from the STATA software program was also used in order to investigate the significance of conversion from MCI to dementia two years after baseline.

Results

Between-group comparison at the first follow-up, one year after baseline

Experimental and control

Mann-Whitney analysis has shown significant differences between the two groups at the first follow-up (Table 3). The experimental group (n=74) outperformed the controls (n=32) in verbal learning ability and digit span ($p \leq 0.031$) (RAVLT) and delayed visual memory ($p=0.005$) (ROCFT). Better performance was also noticed in executive function, namely in prospective memory, accuracy, and goal maintenance ($p \leq 0.008$) (FUCAS). Furthermore, higher performance of the experimental group was found in the daily activities of telephone communication and medication ($p \leq 0.025$) (FUCAS). The general cognitive ($p=0.020$) (TOTAL MMSE) and functional performance ($p=0.003$) (TOTAL

FUCAS), were also better in the experimental group in respect to the control group. Delayed verbal recall, planning, sequence of steps and shopping ability did not differ between the two groups at the end of the first year.

***Table 3**. Between group differences of cognitive and functional performance at the 1st and the 2nd follow-up*

Cognitive/Functional Performance *M (SD)	1st follow-up			2nd follow-up		
	Control Group (n=32)	Experimental Group (n=74)	p	Control Group (n=32)	Experimental Group (n=41)	p
General cognitive function (Total MMSE)	26.75 (2.31)	27.75(1.78)	**0.020**	25.90 (2.65)	28.00 (1.41)	**0.000**
General Functional Performance (Total FUCAS)	45.18 (2.72)	43.60 (1.73)	**0.003**	46.75 (4.91)	42.90 (1.24)	**0.000**
VERBAL MEMORY						
Digit Span (RAVLT)	4.56 (1.96)	5.40 (1.85)	**0.021**	5.03 (2.11)	5.80 (2.45)	0.091
Learning ability (RAVLT)	9.90 (2.92)	11.08 (2.50)	**0.031**	9.56 (3.00)	11.92 (2.64)	**0.000**
Delayed recall (RAVLT)	7.50 (3.27)	8.51 (3.17)	0.087	6.96 (3.47)	9.19 (3.46)	**0.005**
VISUAL MEMORY						
Complex figure delayed recall ROCFT)	10.95 (6.06)	14.89 (6.42)	**0.005**	11.42 (6.42)	16.75 (5.97)	**0.001**
EXECUTIVE FUNCTION						
Planning (FUCAS)	6.18 (.39)	6.08 (.27)	0.111	6.50 (.87)	6.00 (.00)	**0.000**
Prospective memory (FUCAS)	6.96 (.93)	6.51 (.68)	**0.008**	7.12 (1.15)	6.36 (.53)	**0.001**
Accuracy of steps (FUCAS)	6.50 (.67)	6.18 (.42)	**0.006**	6.81 (1.02)	6.12 (.33)	**0.000**
Sequence of steps (FUCAS)	6.09 (.29)	6.01 (.11)	0.079	6.25 (.76)	6.00 (.00)	**0.012**
Goal maintenance (FUCAS)	7.21 (.97)	6.72 (.78)	**0.007**	7.68 (1.11)	6.41 (.54)	**0.000**
DAILY ACTIVITIES						
Telephone communication (FUCAS)	8.76 (2.26)	7.82 (1.12)	**0.025**	9.03 (1.92)	7.58 (.99)	**0.000**
Shopping (FUCAS)	7.62 (1.03)	7.36 (.80)	0.109	8.28 (1.54)	7.21 (.68)	**0.000**
Medication (FUCAS)	7.59 (.97)	7.21 (.62)	**0.019**	7.75 (1.39)	7.09 (.43)	**0.004**

*M (SD) = Mean (Standard Deviation), p = Significant difference of performance between the two groups

Between-group comparisons at the second follow-up, two years after baseline

Comparison between two years training and control group

The group with two years of training (N=41) outperformed the controls in verbal learning ability (p=0.000) and delayed verbal recall (p=0.005) (RAVLT), prospective memory (p=0.001), planning (p=0.000), accuracy (p=0.000), sequence of steps (p=0.012) and goal maintenance (p=0.000) (FUCAS), delayed visual memory (p=0.001) (ROCFT), telephone communication (p=0.000), medication (p=0.004), and shopping (p=0.000) (FUCAS), general cognitive function (p=0.000) (MMSE) and general performance in daily activities (p=0.000) (TOTAL FUCAS) (Table 3).

Comparison between the two-year training and the one-year training

The two-year training group outperformed the one-year training group, in verbal learning ability (p=0.007) (RAVLT), and in delayed visual memory (p=0.007) (ROCFT). Furthermore, higher performance was noticed in executive function specifically in accuracy (p=0.009) and goal maintenance (p=0.004) (FUCAS). The two-year training group also performed better in shopping ability (p=0.009) (FUCAS) and in daily activities (p=0.000) (TOTAL FUCAS) (Table 4).

Table 4. *Between groups differences of cognitive and functional performance (experimental with 2 years training and experimental with one year training) at baseline and two years later, at the second follow-up*

Cognitive/Functional Performance *M (SD)	**Experimental Group with one year training (n=33)**	**Experimental Group with two years training (n=41)**	**p**
General cognitive function (Total MMSE)	27.21 (2.36)	28.00 (1.41)	0.114
General Functional Performance (Total FUCAS)	44.75 (3.03)	42.90 (1.24)	**0.000**
VERBAL MEMORY			
Digit Span (RAVLT)	5.09 (2.37)	5.80 (2.45)	0.080
Learning ability (RAVLT)	10.18 (3.16)	11.92 (2.64)	**0.007**
Delayed recall (RAVLT)	7.57 (4.05)	9.19 (3.46)	0.048
VISUAL MEMORY			
Complex figure delayed recall (ROCFT)	12.54 (7.01)	16.71 (5.97)	**0.007**
EXECUTIVE FUNCTION			
Planning (FUCAS)	6.09 (.29)	6.00 (.00)	0.079
Prospective memory (FUCAS)	6.72 (.91)	6.36 (.53)	**0.**041
Accuracy of steps (FUCAS)	6.60 (.74)	6.12 (.33)	**0.009**
Sequence of steps (FUCAS)	6.06 (.24)	6.00 (.00)	0.189
Goal maintenance (FUCAS)	7.09 (1.01)	6.41 (.54)	**0.001**
DAILY ACTIVITIES			
Telephone communication (FUCAS)	8.39 (1.69)	7.58 (.99)	0.111
Shopping (FUCAS)	7.81 (1.30)	7.21 (.68)	**0.009**
Medication (FUCAS)	7.30 (.84)	7.09 (.43)	0.126

*M (SD) = Mean (Standard Deviation), p = Significant difference of performance between the two groups

Comparison between the one-year training and the control group

The one-year cognitive training group (N=33) performed better than the control group (N=32) in executive function and specifically in planning (p=0.009) and goal maintenance (p=0.013) (FUCAS), in general cognitive function (p=0.016) (MMSE) and in daily activities (p=0.009) (TOTAL FUCAS) (Table 5).

Table 5. Between groups differences of cognitive and functional performance (control group and experimental group with one year of training) at the second follow-up

Cognitive/Functional Performance *M (SD)	Control Group (n=32)	Experimental Group with one year training (n=33)	p
General cognitive function (Total MMSE)	25.90 (2.65)	27.21 (2.36)	**0.016**
General Functional Performance (Total FUCAS)	46.75 (4.91)	44.75 (3.03)	**0.009**
VERBAL MEMORY			
Digit Span (RAVLT)	5.03 (2.11)	5.09 (2.37)	0.482
Learning ability (RAVLT)	9.56 (3.00)	10.18 (3.16)	0.186
Delayed recall (RAVLT)	6.96 (3.47)	7.57 (4.05)	0.229
VISUAL MEMORY			
Complex figure delayed recall (ROCFT)	11.42 (6.42)	12.54 (7.01)	0.281
EXECUTIVE FUNCTION			
Planning (FUCAS)	6.50 (.87)	6.09 (.29)	**0.009**
Prospective memory (FUCAS)	7.12 (1.15)	6.72 (.91)	0.074
Accuracy of steps (FUCAS)	6.81 (1.02)	6.60 (.74)	0.294
Sequence of steps (FUCAS)	6.25 (.76)	6.06 (.24)	0.153
Goal maintenance (FUCAS)	7.68 (1.11)	7.09 (1.01)	**0.013**
DAILY ACTIVITIES			
Telephone communication (FUCAS)	9.03 (1.92)	8.39 (1.69)	0.074
Shopping (FUCAS)	8.28 (1.54)	7.81 (1.30)	0.090
Medication (FUCAS)	7.75 (1.39)	7.30 (.84)	0.078

*M (SD) = Mean (Standard Deviation), p = Significant difference of performance between the two groups

Within-Group Comparison between the baseline assessment and the second follow-up

Experimental group with two years cognitive training

According to the Wilcoxon test the experimental group (N=41) showed improvement in executive function and specifically in goal maintenance (p=0.014) (FUCAS) and also in general performance in daily activities (p=0.020) (TOTAL FUCAS). All of the remaining abilities appeared slightly improved, but there was a ceiling effect that did not permit further significant positive changes (Table 6).

Table 6. Cognitive and functional performance of the Experimental group at the 1st and the 2nd follow up

Cognitive/Functional Performance *M (SD)	One year follow-up (n=41)	Two years follow-up (n=41)	p
General cognitive function (Total MMSE)	27.97 (1.62)	28.00 (1.41)	0.443
General Functional Performance (Total FUCAS)	43.53 (1.55)	42.90 (1.24)	**0.020**
VERBAL MEMORY			
Digit Span (RAVLT)	5.63 (1.90)	5.80 (2.45)	0.418
Learning ability (RAVLT)	11.46 (2.01)	11.92 (2.64)	0.087
Delayed recall (RAVLT)	9.02 (2.62)	9.19 (3.46)	0.173
VISUAL MEMORY			
Complex figure delayed recall (ROCFT)	16.37 (5.91)	16.71 (5.97)	0.349
EXECUTIVE FUNCTION			
Planning (FUCAS)	6.12 (.33)	6.00 (.00)	0.030
Prospective memory (FUCAS)	6.48 (.63)	6.36 (.53)	0.213
Accuracy of steps (FUCAS)	6.17 (.38)	6.12 (.33)	0.363
Sequence of steps (FUCAS)	6.02 (.15)	6.00 (.00)	0.508
Goal maintenance (FUCAS)	6.70 (.71)	6.41 (.54)	**0.014**
DAILY ACTIVITIES			
Telephone communication (FUCAS)	7.80 (1.10)	7.58 (.99)	0.241
Shopping (FUCAS)	7.29 (.71)	7.21 (.68)	0.344
Medication (FUCAS)	7.24 (.66)	7.09 (.43)	0.232

*M (SD) = Mean (Standard Deviation), p = Significant difference of performance between the 1st and 2nd year assessment

The rate of conversion to dementia, 2 years after the initial diagnosis

The rate of conversion to dementia appeared to be significantly different among the groups (x^2=15.360, p≤0.001). None of the 41 participants with two years of training converted to dementia. This was not the case for the controls because: 10 out of 32 patients were diagnosed with dementia, while among the participants with 1 year of training 4 patients were diagnosed with dementia (Table 7).

***Table 7**. People who converted and no converted in dementia*

	Converted	Percent (%)	No converted	Total number
Control Group	10	31%	22	32
Experimental with one year of training	4	12%	29	33
Experimental with two years of training	0	0%	41	41

Discussion

The main aim of our study was to show if the improvement of executive function abilities is possible after long-term focused cognitive training. This aim was partially achieved at the end of the first year of cognitive training. Prospective memory, accuracy of steps and goal maintenance were better than those of the control group. However, planning and sequence of steps did not present any significant change. The experimental group outperformed the control group in verbal learning ability, verbal digit spam, and delayed visual memory. This was a secondary benefit that was achieved through the generalization of the primary cognitive benefit in other cognitive domains. These results are similar to those in others studies [18, 19]. There was also a positive change in the domain of delayed verbal recall but it was not significant. Moreover, the experimental group performed better than the controls in complex daily activities e.g. telephone communication and medication. The transfer of cognitive training in real life is the ultimate goal for a cognitive training attempt and it was already achieved at the end of the first year of training. We did not notice any beneficial change in the domain of shopping. Similar to our results, there are data in other studies confirming the effectiveness of cognitive training in people with MCI [17, 20, 21]. However, apart from the study by Tsolaki et al. in 2011, [17] these studies have not shown that cognitive training can also improve the activities of daily living. In contrast to these studies, our patients improved their functional performance. As it is known, complex daily activities are likely to be impaired early in people with MCI [22] [23] and the worsening of functional and executive function performance has been found to be associated with increased rates of progression from MCI to dementia [24]. The improvement of executive function in daily life was an important result of our study and the possibility to delay the progression from MCI to dementia, through cognitive training of executive function's cognitive parameters was hence confirmed.

At the end of the intervention, the two-year training group significantly outperformed the control group in verbal learning ability and delayed verbal recall, delayed visual memory, executive function (planning, prospective memory, accuracy, sequence and goal maintenance), and complex daily activities (telephone communication, shopping, medication), in general cognitive function and general functional performance. Our data are in agreement with studies concerning the effectiveness of a cognitive intervention [25-28] with a long-term follow-up. However, in these studies, cognitive training was applied in healthy elderly and elderly with memory complaints, not in people with MCI. Furthermore, the short duration of training was one of the possible reasons why they did not show any significant effect in functional performance. In our study, people with MCI managed to transfer the cognitive benefit of training in daily life, partially since the first part of the intervention. This benefit was more evident at the end of the second year, with the improvement of shopping. The

experimental group maintained and further improved executive function abilities, such as planning. The generalization of the primary cognitive benefit was retained and further expanded with the improvement of delayed verbal recall.

There is little research concerning the duration of training necessary for the maintenance or the further development of the cognitive benefits over time [29]. Therefore, we compared the one-year training experimental group with the two-year one, in order to investigate the duration of training which is more beneficial. The comparison at the second year follow-up showed significant differences in favor of the two-year experimental group, in verbal learning, delayed visual memory, accuracy and goal maintenance, shopping ability, and also in general functional performance. These results suggest that, in contrast to the one-year training group, the patients with two years of training maintained the cognitive effect of the training for one more year. To our knowledge, the studies providing data on the effectiveness of training time are few. However, some studies support the idea that there is a dose- dependent relationship between training and generalization, such that more training provides more benefit [30,31]. Thus, we consider that these results are very important since they confirm that longer cognitive training is more beneficial. Finally, two years after the baseline assessment, the one-year training experimental group outperformed the controls in planning and goal maintenance, general cognitive function and general performance in daily activities. These findings support the idea that even one year of cognitive training can be longitudinally more beneficial than no training at all. Our results corroborate other studies which suggest that the benefit of the training is maintained about six months or more, after the completion of the training in people with MCI [20, 25, 32-34]. However, the people with two years of training maintained the benefit achieved during the first year, and they had a further improvement in cognitive and functional domains at the end of the second year.

Moreover, we noticed that two years after baseline, 10 out of the 32 aMCImd controls (31%) and 4 people with aMCImd of the one-year training experimental group slid to dementia. No people of the two-year training group fulfilled the NINCDS-ADRDA dementia criteria at the same time. Various longitudinal studies have attempted to estimate the rate of progression from MCI to dementia, showing that there is great heterogeneity in the conversion rates, which varies from 13% to 48% for a period between 24-30 months [35-38]. This heterogeneity probably indicates that the rate of conversion is affected by the clinical incidence of the first MCI symptoms.

In our sample, the people with two years of training reduced diminished the rate of conversion to dementia. On the contrary, the people with one year cognitive training showed a rate of 12%. This result is in consistence with other studies which show that the annual conversion rates from MCI to dementia often range from 10% to 15% in clinic samples [39]. Consequently, we can suggest that the results of our study are important since they have given us evidence that one year of training is not enough to protect all people with aMCImd from the clinical incidence of dementia, while the two years of training can minimize this conversion rate at least as far as the training is continued.

Conclusion

Our study provides evidence, that two years of cognitive training in people with aMCImd is better than one year of training or no training at all. However, further studies are needed in order to examine both the effectiveness of long-term cognitive training beyond a two-year period, with a larger sample of participants, and the maintenance of the benefit in the absence of training.

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Longitudinal cognitive training program in people with mild Alzheimer's disease: A Randomized Controlled Trial

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Abstract

Objective: This study evaluates the efficacy of a two-year cognitive training program in patients with mild Alzheimer's Disease. Methods: Fifty-five patients with mAD were randomly assigned in o two groups, matched at baseline for age, gender, education, cognitive and functional performance. The experimental group (N=32) attended 160 weekly 2-hour sessions of executive function training for a period of two years. The control group (N=23) did not take part in any program of cognitive training. Neuropsychological assessment was performed at baseline and two years later, at the end of the intervention. Results: At the follow up, the experimental group was better than the control group in: verbal learning (p=0.019), delayed recall (p=0.019), prospective memory (p=0.008), planning (p=0.005), time management (p=0.004), step sequence (p=0.000), taking medication (p=0.005), telephone communication (p=0.009), orientation (p=0.009) and general cognitive (p=0.029) and functional performance (p=0.002). The experimental group showed stability of cognitive performance and improvement in verbal fluency (p=0.002), while the control group deteriorated in episodic verbal memory (p=0.004), prospective memory (p=0.001), planning (p=0.003), time management (p=0.005), taking medication (p=0.004), orientation (p=0.005) and general cognitive (p=0.023) and functional performance (p=0.002). Conclusion: Intense and continuous cognitive training has a long-term effect in patients with mAD, concerning the stabilization of the cognitive and functional performance at least for two years.

Keywords: Alzheimer's Disease, cognitive training, non-pharmacological therapy, two-year intervention, longitudinal study.

Introduction

The rapidly rising aging population is one of the reasons for the progressive increase of neurodegenerative disorders, such as dementia [1]. Alzheimer's disease (AD) is the most frequent reason of cognitive impairment among the elderly [2]. AD is characterized by a gradual decline in a broad range of cognitive domains, such as episodic verbal and visual memory [3], visual constructive abilities [4, 5], language [6], attention and executive function [7, 8]. As a result, the daily function is impaired [9].

Pharmaceutical and non-pharmaceutical therapies are proposed for the management of AD clinical symptoms. Pharmaceutical therapy with cholinesterase inhibitors (ChEIs) seems to enhance, stabilize, and reduce the rate of cognitive decline, in patients with major cognitive impairment [10].

However, pharmaceutical therapy is not possible to modify disease progression [11] but only to provide a mild relief from clinical symptoms. Furthermore, it may not be effective for all patients [12] and the effectiveness lasts only for a few months up to one year, and then, there is a significant progressive decline [13].

Non-pharmaceutical therapy seems to be beneficial for patients with mild AD [14] [15]. It is based on the idea of neuronal plasticity. Even though neuronal plasticity is reduced either with age [16] or due to degenerative diseases [17], it is still partly active in the degenerated brain [18]. Therefore, since cognitive plasticity can be activated through new learning, it is suggested that cognitive training has the potential to help patients with mAD to improve their performance [19]. Cognitive training, one type of non-pharmaceutical therapy, comprises guided practice on a set of standardized tasks and aims to enhance specific aspects of cognition, such as memory, language, attention or executive function [20]. The training of specific skills can improve or at least stabilize performance on of the skills trained [21].

The challenge of cognitive training in AD is how to stabilize the rate of cognitive decline, in order to keep the patient's activities of daily life (ADL) spared. According to some studies, the enhancement of executive function has the potential to maintain the patient's independence for a long time [22].

In the current study we tested the hypothesis that the continuous 2-year intensive cognitive training of executive function abilities could stabilize the cognitive and functional performance of patients with mAD.

Methods

Participants

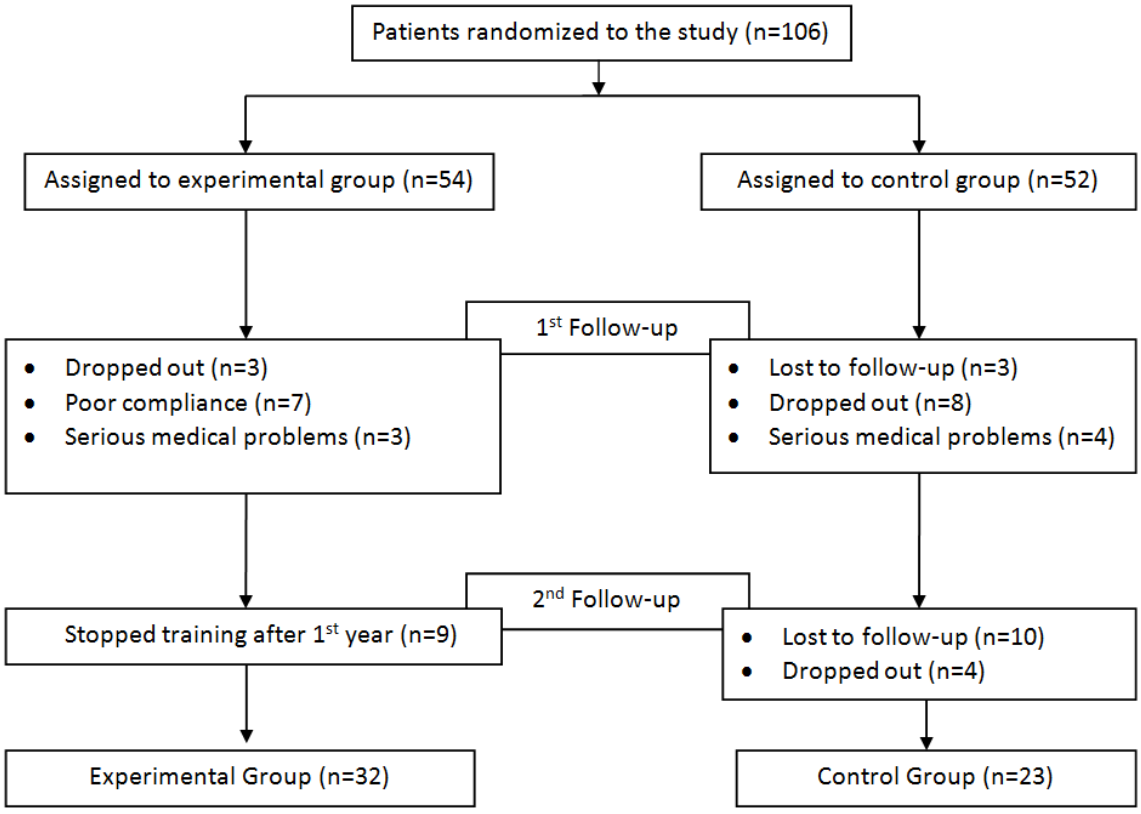
The patients were recruited from the Day Care Unit of Alzheimer Hellas in Thessaloniki, Greece and the study was carried out entirely at the same unit. The study was approved by the Ethics Committee of Democritus University of Thrace and the scientific committee of Alzheimer Hellas. In order to minimize selection bias, the participants of the study were chosen at random by using computer-generated numbers. Both patients and their relatives were adequately informed about the study and gave their written informed consent of participation. They were also aware that they could withdraw their consent at any time without their statutory rights or medical care being affected.

Inclusion criteria comprised Alzheimer's disease diagnosis [23, 24], mild stage of Alzheimer's disease with MMSE score ≥19, cognitive deficits awareness, spared language skills, e.g. speech comprehension and production, and drugs or no drugs therapy with Cholinesterase Inhibitors (ChEIs).

Exclusion criteria were MCI diagnosis [23, 25], severe psychotic traits, untreated depression (Geriatric Depression Scale-GDS ≥6), behavioral problems according to the Neuropsychiatric Inventory (NPI), other neurological disorders such as stroke or ischemic lesions, use of antipsychotics, and sensory deficits e.g. in visual acuity or hearing, which would compromise participation in the study.

The participants were men and women, recruited from June 2013 to September 2015. Out from the 106 patients, who met the inclusion criteria, 54 were randomly assigned in experimental

group and 52 were assigned in control group. Out of the 54 patients of the experimental group, 3 patients dropped out during the first year, 7 patients missed more than 10 sessions , while 3 patients encountered serious medical problems (n=3), and were excluded from the study. Moreover, 9 patients stopped training after the first year. Out of the 52 patients of the control group 3 patients lost to follow-up, 8 dropped out, while 4 were excluded because of serious medical problems. During the second year 10 patients out of the control group were lost to follow-up, while 4 patients were dropped out (Figure 1). Finally, a group of 32 patients with mAD constituted the experimental group, with a mean score in Mini-Mental State Examination (MMSE) 23.25 (*SD*=2.42) and 8.37 (*SD*=4.61) years of education. The control group comprised 23 patients with mAD, with a mean MMSE score 22.21 (*SD* =2.87) and 7.86 (*SD*=3.95) years of education. Baseline characteristics of the participants and their



cognitive and functional performance are presented in Table 1.

Figure 1. Flow chart of the study.

Design

Thirty-two patients with mAD attended a cognitive training program at the day care unit of Alzheimer Hellas. The executive function seems to be correlated with ADL, since better executive function entails maintenance of the patient's independence for more time [22]. Therefore, according to our hypothesis, the aim of the program was the stabilization of the daily function through the training of cognitive executive function parameters, contributing to problem solving, such as: planning, prospective memory, accuracy, sequence, time management and verbal fluency.

Table 1. *Demographic characteristics and baseline participants' cognitive and functional performance (t-test, Pearson's Chi Square exact test)*

Characteristics/Cognitive/Functional Performance M (SD)	**Control group (N=23)**	**Experimental group (N=32)**	**p**
Age	73.00 (7.09)	75.15 (4.87)	0.187
Gender M/F	10/13	6/26	0.071
Years of education	7.86 (3.95)	8.37 (4.61)	0.647
Use of ChEIs (yes/no)	8/15	19/13	0.074
General cognitive performance (MMSE) ‡	22.21 (2.87)	23.25 (2.42)	0.155
General functional performance (FUCAS) †	51.56 (3.71)	52.31 (3.64)	0.430
EPISODIC VERBAL MEMORY			
Learning ability (RAVLT) ‡	5.69 (2.43)	6.40 (1.62)	0.200
Delayed recall ability (RAVLT) ‡	2.17 (2.14)	1.84 (1.79)	0.538
EPISODIC VISUAL MEMORY			
Delayed Visual memory (ROCFT) ‡	4.36 (4.07)	4.56 (3.65)	0.855
EXECUTIVE FUNCTION			
Verbal fluency (FAS) ‡	7.03 (3.24)	7.87 (2.97)	0.321
Comprehension(FUCAS) †	6.47 (.51)	6.40 (.55)	0.628
Prospective memory (FUCAS) †	8.13 (1.17)	8.43 (1.13)	0.334
Planning (FUCAS) †	6.89 (.69)	7.09 (.77)	0.275
Time management(FUCAS) †	6.34 (.57)	6.50 (.67)	0.383
Step sequence (FUCAS) †	6.81 (.95)	6.81 (.78)	0.981
Step accuracy (FUCAS) †	7.86 (1.21)	7.90 (.99)	0.903
Goal completion (FUCAS) †	8.95 (.87)	9.18 (1.11)	0.414
DAILY FUNCTION			
Medication (FUCAS) †	8.43 (1.64)	8.87 (1.69)	0.341
Telephone communication (FUCAS) †	11.39 (2.25)	10.84 (1.91)	0.336
Shopping (FUCAS) †	8.65 (1.66)	9.46 (2.12)	0.131
Personal hygiene (FUCAS) †	7.00 (.00)	7.00 (0.00)	0.388
Orientation (FUCAS) †	8.95 (1.33)	9.09 (1.94)	0.771
Clothing (FUCAS) †	7.17 (.57)	7.00 (0.00)	0.092

*M (SD) = Mean (Standard Deviation) ‡= More points/better performance

p = Statistical difference of performance †= Less points/better performance

Intervention

The cognitive training sessions were carried out in groups of 8-10 patients. They were conducted by a trained cognitive psychologist. The cognitive training included two sessions per week, each of which lasted two hours, with a break of 15 min in between them. The patients had to visit the day care unit twice a week for two years, with a 2 weeks' break for Christmas vacations, a 2 weeks' break for Easter and a 4 weeks' break for summer. Therefore, they had to complete 80 sessions (160 hours) per year. The cognitive tasks of each session were ecologically valid as they were derived from ADL and they were not similar to the tasks included in the neuropsychological tests. The weekly sessions included:

1. One hour of RHEA cognitive training through motor instructions. The patients used learning and memory strategies in order to remember the instructions of the therapist. They were asked to perform specific motor activities enrolling abilities of attention and executive function [26].

2. One hour of Peter Pan. Cognitive training through playing: Executive function and attention abilities were trained using toys, such as dolls, puzzles, plastic letters, plastic animals and fruits. For example, the patients had to collect plastic fruits and categorize them according to season, or color

or size. Then, they were asked to find words beginning with by the first letter of the fruit they had collected.

3. One hour of Dance and Drama therapy. The patients were encouraged to dance and play different roles in order to train executive function abilities, such as planning, step sequence and accuracy, as well as abstract thinking. They were trained to organize the steps they needed to perform in order to solve a daily problem, such as "What do I have to do if I lose my wallet?" The dancing task also activated their abstract thinking, as they were asked to answer simple questions concerning the lyrics of the song they were listening while dancing.

4. One hour of Reality Orientation in Current Events. This program focused on a structured discussion of daily social events. It trains executive function abilities and enhances socialization. The patients watched a video concerning a current social event. They had to answer specific questions related to the video and express their own opinion.

Neuropsychological assessment

All participants were assessed at baseline and two years later, at the end of the intervention. Each participant was evaluated by a neuropsychologist, blinded to the patient's group allocation. Tests assessing executive function abilities, such as verbal fluency, comprehension, prospective memory, planning, time management, step sequence and accuracy and goal completion were used in order to identify the patients' performance at the follow up concerning the trained abilities. Tests of visual and verbal memory were included in the battery in order to evaluate the possible effect of the training in other cognitive domains through the process of generalization. The assessment of ADL, such as taking of medication, telephone communication, shopping, personal hygiene, orientation and clothing was also conducted since this performance was the ultimate goal of the intervention. The whole neuropsychological battery is presented in Table 2 [27].

Table 2. *Neuropsychocological battery for the measurement of cognitive and functional abilities*

Ability	Tests	Measures
General cognitive function	Mini Mental State Examination (MMSE) (Folstein 1975; Fountoulakis 2000)	Total raw score‡
General Functional performance	Functional Cognitive Assessment Scale (FUCAS) (Kounti 2006)	Total raw score†
Verbal learning	Rey Auditory Verbal Learning test (RAVLT) (Rey 1958)	Learning ability‡
		Delayed recall ‡
Visual memory	Rey Osterrieth Complex Figure Test (ROCFT) (Rey 1941)	Complex figure delayed recall‡
	Verbal fluency (FAS) Tombaugh, T. N., Kozak, J., & Rees, L. (1999)	Total raw score‡

Executive function	Functional Cognitive Assessment Scale (FUCAS) (Kounti 2006)	Comprehension† Prospective memory † Planning† Time management† Step sequence † † Step accuracy† Goal completion†
Daily activities	Functional Cognitive Assessment Scale (FUCAS) (Kounti 2006)	Medication† Telephone communication† Shopping† Personal hygiene† Orientation† Clothing†

‡= More points/better performance †= Less points/better performance

Statistical analysis

The analysis was performed with the SPSS statistical software, version 21.0. Demographic, cognitive and functional characteristics at baseline were analyzed using a two tailed *t* test for independent samples or a two sided chi-square when it was necessary. Univariate analysis (ANCOVA) controlling for drugs (ChEIs) was used in order to examine the between-group differences at the follow-up. The effect of cognitive training was analyzed with repeated measures analysis of variance (ANCOVA), also controlling for drugs (ChEIs). Statistical significance was set using Bonferroni correction. In order to calculate the magnitude of the cognitive training effects on the experimental group, we calculated standardized effect sizes for each neuropsychological measure.

Results

It should be stressed that according to the *t* test at baseline there were no statistically significant differences between the two groups in age (p= 0.187), education (p= 0.647) or gender (p= 0.071), nor in cognitive or functional performance (Table 1).

At the follow-up, the analysis of variance showed that the experimental group was better than the control group in prospective memory (p= 0.008, F= 7.699), planning (p= 0.005, F= 8.609), time management (p= 0.004, F= 9.102), and in step sequence (p= 0.000, F= 15.784). Higher performance in favor of the experimental group was also noticed in verbal learning (p= 0.019, F= 5.820), verbal delayed recall (p= 0.016, F= 6.228), ADL especially in medication (p= 0.005, F= 8.603), telephone communication (p= 0.009, F= 7.417) and orientation (p= 0.009, F= 29.147). Finally,

the experimental group performed better in general cognitive (p= 0.029, F= 5.071) and ADL (p= 0.002, F= 10.200) (Table 3).

Table 3. *Between group differences of cognitive and functional performance at follow-up (after two years)*

Cognitive/Functional Performance M (SD)	**Control group (N=23)**	**Experimental group (N=32)**	**p**	**F**
General cognitive performance (MMSE) ‡	19.39 (4.56)	22.06 (3.50)	**0.029**	5.071
General functional performance (FUCAS) †	59.34 (7.99)	53.21 (5.56)	**0.002**	10.200
EPISODIC VERBAL MEMORY				
Learning ability (RAVLT) ‡	4.91 (2.23)	6.40 (2.18)	**0.019**	5.820
Delayed recall ability (RAVLT) ‡	.91 (1.47)	2.28 (2.47)	**0.016**	6.228
EPISODIC VISUAL MEMORY				
Delayed Visual memory (ROCFT) ‡	3.50 (3.96)	4.23 (3.69)	0.558	0.348
EXECUTIVE FUNCTION				
Verbal fluency (FAS) ‡	6.49 (3.12)	8.82 (3.02)	0.017	6.028
Comprehension (FUCAS) †	6.91 (1.08)	6.34 (.74)	0.041	4.371
Prospective memory (FUCAS) †	9.56 (1.53)	8.59 (1.18)	**0.008**	7.699
Planning (FUCAS) †	8.17 (1.58)	7.00 (1.16)	**0.005**	8.609
Time management(FUCAS) †	7.52 (1.20)	6.59 (.91)	**0.004**	9.102
Step Sequence(FUCAS) †	8.04 (1.30)	6.65 (1.09)	**0.000**	15.784
Step accuracy (FUCAS) †	9.08 (1.34)	8.62 (1.45)	0.210	1.612
Goal completion (FUCAS) †	10.00 (1.78)	9.50 (1.10)	0.233	1.459
DAILY FUNCTION				
Medication (FUCAS) †	10.69 (2.47)	9.21 (1.79)	**0.005**	8.603
Telephone communication (FUCAS) †	12.56 (2.44)	10.87 (2.05)	**0.009**	7.417
Shopping (FUCAS) †	10.60 (3.73)	9.53 (2.50)	0.425	0.642
Personal hygiene (FUCAS) †	7.04 (.20)	7.00 (.00)	0.143	2.214
Orientation (FUCAS) †	10.86 (2.30)	9.43 (1.68)	**0.009**	29.174
Clothing (FUCAS) †	7.52 (1.08)	7.06 (.35)	0.032	4.855

M (SD) = Estimated means (Standard Deviation) calculated with ANCOVA , p = Statistical difference of performance, F = Effect sizes, ‡= More points/better performance, †= Less points/better performance

According to the repeated measures analysis of variance at the follow-up, the experimental group showed improvement in verbal fluency (p= 0.002, F= 11.787), while the rest of the cognitive and functional abilities were preserved. The control group showed deterioration in prospective memory (p= 0.001, F= 13.912), planning (p= 0.003, F= 10.976), time management (p=0.005, F=9.737), medication (p= 0.004, F= 10.780) and orientation (p= 0.005, F= 9.730). Verbal delayed recall was further compromised as well (p= 0.004, F= 10.254). Decline was also noticed in general cognitive (p= 0.023, F= 5.993) and ADL performance (p= 0.002, F= 12.761) (Table 4).

Table 4. *Cognitive and functional performance of the control and the experimental group at baseline and*

at follow-up

	Control group (N=23)				Experimental group (N=32)			
Cognitive/Functional Performance	**Baseline**	**Follow-up**	**p**	**F**	**Baseline**	**Follow-up**	**p**	**F**
M (SD)								
General cognitive performance (MMSE) ‡	22.21 (2.87)	19.39 (4.56)	**0.023**	5.993	23.25 (2.42)	22.06 (3.50)	0.410	0.697
General functional performance (FUCAS) †	51.56 (3.71)	59.34 (7.99)	**0.002**	12.761	52.31 (3.64)	53.21 (5.56)	0.723	0.128
EPISODIC VERBAL MEMORY								
Learning ability (RAVLT) ‡	5.69 (2.43)	4.91 (2.23)	0.110	2.793	6.40 (1.62)	6.40 (2.18)	0.345	0.930
Delayed recall ability (RAVLT)‡	2.17 (2.14)	.91 (1.47)	**0.004**	10.254	1.84 (1.79)	2.28 (2.47)	0.156	2.113
EPISODIC VISUAL MEMORY								
Delayed Visual memory (ROCFT) ‡	4.36 (4.07)	3.50 (3.96)	0.407	0.717	4.56 (3.65)	4.23 (3.69)	0.083	3.202
EXECUTIVE FUNCTION								
Verbal fluency (FAS) ‡	7.03 (3.24)	6.49 (3.12)	0.390	0.771	7.87 (2.97)	8.82 (3.02)	**0.002**	11.787
Comprehension(FUCAS) †	6.47 (.51)	6.91 (1.08)	0.084	3.229	6.40 (.55)	6.34 (.74)	0.146	2.230
Prospective memory (FUCAS) †	8.13 (1.17)	9.56 (1.53)	**0.001**	13.912	8.43 (1.13)	8.59 (1.18)	0.254	1.352
Planning (FUCAS) †	6.89 (.69)	8.17 (1.58)	**0.003**	10.976	7.09 (.77)	7.00 (1.16)	0.645	0.210
Time management(FUCAS) †	6.34 (.57)	7.52 (1.20)	**0.005**	9.737	6.50 (.67)	6.59 (.91)	0.034	4.935
Step sequence(FUCAS) †	6.81 (.95)	8.04 (1.30)	0.020	6.392	6.81 (.78)	6.65 (1.09)	0.831	0.046
Step accuracy (FUCAS) †	7.86 (1.21)	9.08 (1.34)	0.033	5.233	7.90 (.99)	8.62 (1.45)	0.089	3.009
Goal completion (FUCAS) †	8.95 (.87)	10.00 (1.78)	0.019	6.489	9.18 (1.11)	9.50 (1.10)	0.703	0.148
DAILY FUNCTION								
Medication (FUCAS) †	8.43 (1.64)	10.69 (2.47)	**0.004**	10.780	8.87 (1.69)	9.21 (1.79)	0.625	0.244
Telephone communication (FUCAS) †	11.39 (2.25)	12.56 (2.44)	0.066	3.773	10.84 (1.91)	10.87 (2.05)	0.088	3.103
Shopping (FUCAS) †	8.65 (1.66)	10.60 (3.73)	0.060	3.951	9.46 (2.12)	9.53 (2.50)	0.706	0.145
Personal hygiene (FUCAS) †	7.00 (.00)	7.04 (.20)	1.000	0.000	7.00 (.00)	7.00 (.00)	0.114	2.655
Orientation (FUCAS) †	8.95 (1.33)	10.86 (2.30)	**0.005**	9.730	9.09 (1.94)	9.43 (1.68)	0.174	1.936
Clothing (FUCAS) †	7.17 (.57)	7.52 (1.08)	0.269	1.126	7.00 (.00)	7.06 (.35)	0.124	2.500

M (SD) = Mean (Standard Deviation) ‡= More points/better performance

p = Statistical difference of performance †= Less points/better performance

F = Effect sizes

Discussion

Our hypothesis that a two-year intense, consistent and continuous participation in a well-structured executive function training could stabilize cognitive performance and ADL of patients with mAD was supported. There was a statistically significant difference in favor of the experimental group in executive function abilities and general cognitive and ADL performance. The difference between the groups was due to the fact that the experimental group stabilized their cognitive and ADL performance, whereas the control group showed significant deterioration. Specifically, a broad range of cognitive abilities, such as executive function, verbal memory and general cognitive performance of the control group were hampered. The deterioration in parameters of executive function, especially in prospective memory, planning and time management, has probably contributed to the deterioration of ADL, since executive function and instrumental ADL are closely related [28]. At the follow-up, the control group had greater difficulty than initially to take medication at the right time or take the right dose per day, to orientate in usual and familiar places and to organize the appropriate steps for a telephone communication. Our findings suggest that the control group had partially lost a significant part of independence, which is associated with ADL. Our results corroborate other studies which confirm patients with mAD with no cognitive training show deterioration in verbal memory,

executive function and ADL [29-31].

The ADL of the experimental group were well preserved. The long-term maintenance of instrumental and basic ADL is the ultimate goal of cognitive rehabilitation, since AD is a neurodegenerative disease basically characterized by a progressive cognitive and functional decline. Similar to our results, there are data in other studies confirming that cognitive training is effective for patients with mAD, since it delays the progression of cognitive impairment [32] and transfers the effectiveness of training in ADL [33, 34]. However, these studies provide data following short time training, ranging from a few weeks to a few months. To our knowledge, few studies provide data on the long-term effectiveness of cognitive training in mAD both in ADL and cognitive abilities for two or more years. Actually, the Requena, Maestu, Campo, Fernandez, and Ortiz study in 2006 [35] investigated the efficacy of pharmaceutical or non-pharmaceutical treatment (cognitive stimulation) for a two-year period in mAD patients. According to their results, the cognitive stimulation group improved their general cognitive performance throughout the first year of the intervention; however, it gradually deteriorated during the second year, reaching the initial cognitive level. Likewise, the longitudinal study of Andersen, Viitanen, Halvorsen, Straume, Wilsgaard, and Engstad in 2012, [36] also showed that after one year of cognitive stimulation and drug therapy there was a stabilization in general cognitive performance.

Contrary to the previous studies, in our study the experimental group not only did they stabilize their cognitive performance but also stabilized ADL, and–further improved their verbal fluency. This probably occurred because our study was based on the principles of cognitive training. Our training program included intense training targeting executive function abilities, while the above mentioned studies comprised stimulation training like walking, book reading, dancing, doing puzzles, etc. Therefore, since cognitive training is more effective than cognitive stimulation [33], we consider that this was the reason for the long-term stabilization.

Conclusions

Our results allow us to conclude that the combination of RHEA, PETER PAN, DANCE AND DRAMA THERAPY, and ORIENTATION IN CURRENT EVENTS provided a systematic, consistent, intense, goal-oriented and long-term cognitive training of executive function which proved to be beneficial for patients with mAD. This may be a promising approach to stabilize ADL as long as possible.

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Reversible and irreversible dementia with psychotic symptomatology as first manifestation

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Abstract

Dementia is a syndrome of generalized cognitive dysfunction in more than two cognitive domains (language, memory, judgment, orientation, e.t.r), without disturbance of attention and consciousness. There are many causes of dementia, both reversible and irreversible. One should always exclude treatable causes before attribute the cognitive decline to irreversible states. Sometimes dementia could start with psychotic manifestations that are misleading to correct diagnosis. One should have in mind to exclude the following entities (disorders) when the leading symptoms are dementia with psychosis, before attributing the whole setting to a psychiatric disease: From irreversible causes of dementia: 1. Primary neurodegenerative syndromes [Alzheimer's disease (AD) with psychosis, Lewy Body disease (LBD), frontotemporal dementia (FTD), and Huntigton's disease (HD)], 2. Central nervous system (CNS) infections [Creutzfeldt-Jacob disease (CJD), neurosyphilis, and AIDS dementia complex). From reversible causes of dementia: 1. Metabolic disorders (hypothyroidism, vitamin B_{12} deficiency), 2. Dementia due to neoplastic and paraneoplastic syndromes (brain tumors, paraneoplastic encephalitis).

Herein, the above mentioned disorders are briefly discussed. Specifically, the present review is focused on those psychotic symptoms of irreversible and reversible disorders which could be misleading to an incorrect diagnosis and should be readily identified on the basis of a detailed clinical history and investigative studies in order to avoid permanent lesions and to secure better quality of life both for patients and caregivers.

Keywords: reversible dementia, irreversible dementia, psychotic symptomatology

Introduction

Dementia is a syndrome with generalized impairment of cognitive function that is usually progressive and irreversible. While the vast majority of the patients have a condition that is not treatable, a small fraction of them have disorders that could reverse by treatment (e.g. vitamin B_1 or B_{12} deficiency, depression, brain space-occupying lesions). A considerable effort should be made to exclude reversible causes of dementia, such as intracranial mass lesion, hypothyroidism, B_{12} deficiency, normal pressure hydrocephalus, or even depression. Most of reversible conditions that present with cognitive impairment or dementia are easily identified by history, psychiatric evaluation and laboratory tests (blood, brain CT or MRI). When the first manifestation of demented people is a psychotic symptomatology the correct diagnosis could be missed. Of paramount importance is to unravel such disorders early in the course of the disease, in order to avoid irreversible lesions of the

central nervous system (CNS) and useless or potentially harmful pharmaceutical intervention to the patient.

A. Irreversible dementias

Decline of cognition from a previous level of functioning without impairment of consciousness is the main characteristic of irreversible dementia. The DSM-IV diagnostic criteria require for the diagnosis: 1. Memory impairment, 2. At least one of the following: aphasia, apraxia, agnosia, disturbance in executive functioning, 3. Disturbance in 1 and 2 interferes with daily functioning and 4. Cognitive deficits are not due to other causes [1]. Dementia occurs more commonly in the elderly than in the younger individuals. Age is a risk factor for AD [2]. AD usually starts near age 65 and increases afterwards as the population ages.

There is a wide variety of neurodegenerative disorders with different patterns of cognitive deficits that one should have in mind to improve differential diagnosis among them [3].

Psychiatric features could be an early symptom of many neurodegenerative conditions, including HD, CJD, diffuse DLB and FTD [4].

Neuropsychological testing is very helpful to distinguish among individuals with a neurodegenerative disease and those with pseudodementia due to major depression, personality disorders and malingering, conversion disorders and psychosis [5].

Neuropsychological assessment evaluates the following domains of patient's cognition: attention and processing speed, memory (encoding, retention and retrieval), visuospatial and constructional abilities, language, and executive functions [6]. There is a wide variety of neuropsychological tests for cognitive evaluation. No single neuropsychological test could differentiate between dementia groups. The accurate interpretation of these tests requires a careful clinical history and the use of adequate tests and norms [6]. When a non-organic (psychiatric) cause is suspected then one should use special neuropsychological scales to detect depression and anxiety, agitation and apathy, hallucinations or delusions.
Differences in the profiles of cognitive deficits associated with AD and other more common neurodegenerative diseases (i.e. FTD, DLB, VaD, HD) are shown in table 1.

Table 1. *Main differences among irreversible types of dementia*

	Onset	Abnormal movements	Behavioral changes	Memory	Language - speech functions

ALZ	> 60 y insidious	No until late stages	Lack of interests, poor judgment, withdrawn, depression	First short-term-then long-term loss, severe	Loss of verbal fluency, worse semantic fluency
DLB	Insidious	Parkinsonism: bradykinesia, rigidity, masked faces, myoclonos	Hallucinations, delusions, REM sleep disturbance	Less severe than AD, bradyphrenia, fluctuations	Hypophonia, soft voice
FTD	Insidious < 60 y	Later on the course gait apraxia. Maybe + amyotrophic lateral sclerosis	Severe: dis-inhibition, apathy, loss of insight	Less severe than AD: impaired retrieval	Severe impairment of speech output, letter and verbal fluency
VaD	Abruptly, subacute	Hemiparesis, focal neurological deficits	Depression, personality changes	As in FTD, stepwise	Slurred speech, less impairment
HD	Insidious 30s-40s	Chorea, oculomotor-gait disturbance	Anxiety, irritability, depression, apathy	Mild to moderate deficits	Slowness of thought, letter and category fluency impairment

I. Primary neurodegenerative syndromes

1. Alzheimer's disease (AD) with psychosis

Alzheimer's disease is the most common cause of dementia. It accounts for 50% -70% of demented patients [7].

It starts slowly and progresses always in the course of the disease [8]. AD with psychosis seems to be a different entity [9]. Depression is present in the earlier stages of the disease in about 25% of the cases. Later on psychiatric symptoms (psychosis with paranoia, hallucinations and delusions) are predominant in the clinical picture. Agitation and negative symptoms are the most difficulty controlling symptoms and they have a worse impact on patients' and caregivers' life [10]. There are no psychotropic medications approved by the FDA for the treatment of psychosis of AD. However, atypical antipsychotic are preferred, but one has to balance against the risk of adverse events in each individual patient [11].

The brain CT/MRI scans show more extended cortical atrophy in patients with psychotic symptoms compared to non-psychotic ones [12]. The [18F] FDG PET scan shows significant metabolic changes

in neocortical association areas [13].

2. Lewy Body disease (DLB)

DLB is a primary degenerative dementia. In DLB, Lewy bodies are found both in cortical and subcortical areas of the brain. Lewy bodies are structures containing filamentous protein called α-synuclein [14]. DLB patients have symptoms both of AD's disease and Parkinson's disease. Core features of DLB are fluctuating cognitive function (50-75%), recurrent visual hallucinations, delusions with aggression and features of parkinsonism (rigidity and bradykinesia, but tremor is less common) (25-50%) [15]. Gait disorder becomes apparent with short, slow, shuffling steps, wide base and difficulty in initiating walking. In addition, psychotic symptoms occur early in DLB and agitation and aggressive behavior may follow. Other symptoms such as REM sleep behavior disorder with vivid dreams, insomnia, depression, central sleep apnea or obstructive sleep apnea may exist. Sensitivity to neuroleptic drugs, often falls and severe autonomic dysfunction are profound in DLB [16]. Rigidity with gait disorder and mask face are core symptoms to make us suspicious about the diagnosis. It is very difficult to make the final diagnosis and there are no tests to confirm, except from brain autopsy [17]. Treatment with small doses of antipsychotics and dopamine agonists could worsen rigidity and psychosis, respectively, and must be used with caution. Besides, there is no doubt that atypical antipsychotic drugs alleviate the psychotic symptoms and improve patients' quality of life, as well as decrease caregiver burden and the need for institutionalization [18]. Cholinergic replacement therapy and selective serotonin reuptake inhibitors (SSRIs) may alleviate patients' amnesia and depression [19, 20].

3. Frontotemporal dementia (FTD)

There are 3 variants of FTD: frontal (behavioral variant), semantic dementia, and progressive non-fluent aphasia [21, 22].

Social disruptive behavior, memory impairment, repetitive speech, hyperorality, incontinence, rigidity or muscle weakness are some of the frontal variant of the disease. Progressive loss of word meaning is the core feature of semantic dementia. Prosopagnosia may also be present as well as behavioral signs in this variant of FTD. In progressive non-fluent aphasia patients lose the power to converse and finally they become mute. Memory and visual orientation are less disturbed [23].

The differential diagnosis from AD is not easy with bilateral atrophy of frontal and temporal lobes being more prominent in FTD. Pick cells and pick bodies are the core structures in FTD [24].

No therapy can help patients with FTD. SSRIs and antipsychotic drugs in small doses could improve behavioral changes. Cholinergic replacement therapy does not help and is not recommended [25, 26].

4. Huntington's disease (HD)

George Huntington first described the disease that bears his name. HD is inherited in an autosomal dominant manner [27]. The disease is progressive, starting at the 4th or 5th decade of life with memory problems, apathy, depression and irregular short, abrupt muscle movements called chorea

[28]. Psychiatric symptoms and intellectual changes can appear before abnormal movements and progressively deteriorate. Dementia and memory disturbances could precede chorea in about one-fourth of cases, but ultimately both are present. Patients' history, laboratory studies and family history can help in differential diagnosis of HD from other conditions associated with dementia and chorea [27, 28]. There is no cure for HD. Dopamine receptor-blocking drugs and drugs depleting dopamine from nerve terminals may be of benefit in controlling the abnormal movements and aggressive behavior [29, 30].

II. Central Nervous System (CNS) infections

1. Creutzfeldt-Jacob disease (CJD)

CJD is the most common human form of a group of rare, fatal brain disorders known as prion diseases. CJD is characterized by rapidly progressive dementia (decline in thinking and reasoning), confusion, difficulty walking, ataxia, mood changes, involuntary muscle movements (myoclonos often induced by startle) and extrapyramidal signs (rigidity, tremor, dystonia, chorea or athetosis) [31]. There are 4 types of the disease [32]: **a. Sporadic CJD**: It accounts for 85 percent of cases. It appears between ages 60-65. CJD progresses rapidly and those affected by sporadic CJD die within one year. **b. Familial CJD**: this form accounts for about 10 to 15 percent of cases. Changes in the prion protein gene lead to a misfolding protein into an abnormal three-dimensional shape which destroys brain cells. There are more than 50 prion protein mutations in those with inherited CJD. **c. Infectious CJD**: It accounts for 1 percent of CJD cases and results from exposure to an external prion protein. Iatrogenic CJD is caused by medical procedures transmitting the prion protein (human tissues transplants, neurosurgery, growth hormone from human sources). d. **Variant CJD:** consumption of products from infected animals results in this type of the disease.

The differential diagnosis involves other types of rapidly progressing dementia, such as acute metabolic disorders and sedative drug withdrawal [33]. Laboratory studies with EEG (triphasic waves of sharp outline that occur about once every second), and CSF (14-3-3 protein elevation) are helpful for diagnosis [34]. Definite diagnosis is by brain biopsy. There is no treatment that can slow or stop the underlying brain cell destruction, caused by CJD and other prion diseases [35].

2. Neurosyphilis

It used to account more than 20% of dementia cases before the use of antibiotics especially penicillin. It occurs 10-15 years after the primary spirochetal infection and affects about 5% of the untreated patients. Gradual deterioration of memory, changes of personality, depression, psychosis, and grandiosity are prominent features of the clinical picture [36]. The terminal stages may include seizures, recurrent strokes, incontinence, pyramidal and extrapyramidal signs [36, 37]. Serological and CSF studies are essential for establishing the diagnosis. Treponemal tests (serum FTA-ABS and MHA-TP) are positive in all patients with active neurosyphilis, as well as non-treponemal (VDRL and RPR) CSF serologic tests. The main therapy of neurosyphilis is aqueous penicillin G [38]. After treatment for general paresis patients may improve or continue to deteriorate.

3. AIDS dementia complex

Human immunodeficiency virus (HIV) is invading the brain and causes subacute encephalitis or acquired immune deficiency syndrome (AIDS) encephalopathy. AIDS dementia may be the first manifestation of AIDS, but more common the onset is insidious and dementia is apparent in late stages of the disease. In the early stages cognitive (memory deficits, forgetfulness, impaired judgment), and behavioral symptoms (apathy, personality changes) are prominent, following by pyramidal signs, extrapyramidal symptoms, cerebellar ataxia, myoclonus, seizures, and organic psychosis (delusions, hallucinations) [39]. Serological (HIV antibodies), and CSF studies (HIV DNA, HIV RNA, moderate elevation of protein, mononuclear pleocytosis and oligoclonal bunds) are essential for establishing the diagnosis [40]. There is no definite treatment at this stage of the disease.

B. Common causes of reversible dementia

Reversible causes of dementia are of paramount importance since they are treatable and reversible if timely diagnosed. The reported frequency varies from 0 to 23% [5]. The prevalence rate of reversible dementia varies according to the population under study. It is more common among younger than 60 years of age individuals, but fairly less in older ones aged more than 65 years [41]. A metanalysis performed by A.M. Clarfield concluded that reversible dementias are much scarcer than previously reported. Potentially reversible causes were seen in 9%, and only 0.6% of dementia cases actually reversed (0.29% partially, and 0.31% fully) [42]. There is a decrease in the prevalence of reversible dementias and this may reflect a better and more careful diagnostic assessment by general practitioners and primary care physicians [43].

Clinical history, neurologic examination paraclinical investigations and comorbid conditions differ between irreversible and reversible dementias (Table 2) [44].

***Table 2**. Main differences of reversible and irreversible dementias with respect to clinical, laboratory investigations and comorbid conditions*

Type of dementia	Age	Clinical history-Neurologic	Comorbid conditions (depressionhypo-T4)	Laboratory investigations	Special investigations (EEG, MRI, CT,

		examination			**CSF, auto-AB, HIV, AB)**
Irreversible (ALZ, FTD, DLB, VaD, HD, CJD)	> 60	Relevant - May be normal at first presentation	May not be relevant to dementia	Maybe normal	Abnormal-Relevant to the disease
Reversible (NPH, metabolic, nutritional, endocrine, CNS infections, tumor, psychiatric disorders, subdural hematoma drugs/toxins)	< 60	Relevant – signs and symptoms of underling medical condition	Fitting to reversible dementias	Abnormal-relevant to the type of dementia	Relevant to reversible types of dementia

I. Causes of dementia of metabolic origin

1. Hypothyroidism

Hypothyroidism usually manifests by cognitive retardation, confusional state, coma or dementia. Common manifestations in severe long lasting hypothyroidism (myxedema madness) are chronic psychosis with delusions and hallucinations, psychomotor retardation, depression, paranoia, mania, and suicide ideation [45]. Characteristic neurologic symptoms pointing to hypothyroidism as a cause of dementia are delayed relaxation of the tendon reflexes, headache, tinnitus, hearing loss, vertigo, paresthesia, dysarthria, or cerebellar ataxia [46, 47]. Laboratory investigations reveal thyroid gland dysfunction (low T3 and T4 levels and elevated TSH). Hypercholesterolemia, hyponatremia, and hypoglycemia may also coexist [48]. Treatment replacement with levothyroxine (T4) is very important to reverse all the above mentioned symptoms.

2. Vitamin B_{12} deficiency

Organic psychosis (paranoid psychosis with hallucinations, depression, mania) and reversible dementia (mental slowness, memory deficits) are common manifestations in vitamin B_{12} deficiency, and may precede or follow hematologic abnormalities (macrocytic anemia) and neurologic dysfunction [49]. Neurological disorders that could accompany B_{12} deficiency include peripheral neuropathy, visual loss (amblyopia), and subacute combined degeneration of the spinal cord (spastic paraparesis with extensor plantar responses, loss of tendon reflexes, vibratory and joint position sense impairment) [50]. Diagnosis of B_{12} deficiency is not difficult when spinal cord disease and anemia coexist with cognitive dysfunction. Treatment requires prompt intramuscular administration of B_{12} for a long duration of time. Reversion of neurologic consequences of B_{12} deficiency depends upon their duration and severity [51, 52].

II. Neoplastic and Paraneoplastic syndromes

1. Brain tumors

Brain tumors (either primary or metastatic into the brain), may manifest with behavioral changes and cognitive decline in addition to their local and diffuse effects, such as edema, increased intracranial pressure, and focal neurologic signs. Dementia due to brain tumors is characterized by mental slowness, memory deficits, apathy, aphasia, agnosia, and personality changes [53, 54, 55]. Cognitive dysfunction may precede any other neurologic deficits. CT scan and MRI are required for making diagnosis, treatment and prognosis of brain tumors. If this is impossible brain biopsy is required. A high degree of vigilance is required for symptoms suggestive of brain tumor, in order not to lose time about definite diagnosis [56].

2. Paraneoplastic encephalitis

Paraneoplastic syndromes of the nervous system occur when the immune system attacks not only cancer but also other parts of the brain, spinal cord, peripheral nerves and muscles [57, 58]. Cancer of lung, ovarian, breast, testis and lymphatic system are more prone to manifest paraneoplastic syndromes. Neurological disorders are recognized as paraneoplastic syndromes only when there is a definite or probable association with cancer. Paraneoplastic syndromes can cause symptoms that resemble dementia. Limbic encephalitis and encephalomyelitis are both paraneoplastic syndromes affecting limbic system and areas of the brain involved with memory and thinking. Patients may experience personality changes, mood disturbances, memory loss, dementia, seizures, vision problems, sleep disturbances, and hallucinations [59, 60]. Paraneoplastic antibodies in blood and CSF and imaging tests are used to identify a tumor causing the symptoms [61, 62, 63]. Treatment of the neurological paraneoplastic syndrome depends on the type of cancer and the removal of the underlying cancer [64, 65].

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Use of Flavonoids in the Development of Antioxidant Nanotechnology against Alzheimer's disease

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Abstract

Neuronal connectivity, which enables learning and memory, degrades progressively during central nervous system (CNS) neurodegenerative pathological conditions such as Alzheimer's disease (AD). Cu(II)-mediated oxidative stress has been shown to play a pivotal role in regulating redox reactions leading to formation of reactive nitrogen/oxygen species, major culprits in AD. The antioxidant properties of flavonoids including catechin (Ct) in neurodegenerative processes have been well-documented. However, the activity that Ct encapsulation in nanoparticles (NPs) may bear on neuronal survival and morphological connectivity has been poorly demonstrated. To investigate potential effects of nano-encapsulated Ct on hippocampal survival and synaptic morphology in primary rat neurons, PEGylated-modified silica NPs and the modified silica NPs with Cetyl trimethylammonium bromide (CTAB) were synthesized. Therefore, Ct was loaded on silica NPs in a concentration-dependent fashion, and release studies were carried out using UV-Visible spectroscopy. Further physicochemical characterization of the novel nano-materials included elemental analysis, particle size, z-potential, Fourier transform infrared spectroscopy (FT-IR), Brunauer-Emmett-Teller (BET), Thermogravimetric analysis (TGA), and scanning electron microscope (SEM) analysis in order to optimize material composition linked to the delivery of loaded catechin in the hippocampal cell milieu. Overall, the findings reveal that, under Cu(II)-induced oxidative stress, the loading ability of the PEGylated/CTAB silica NPs is concentration-dependent, based on their Ct release profile. The whole bio-activity profile of the new hybrid NPs a) denoted their enhanced protective activity against oxidative stress as well as hippocampal cell survival in comparison to controls, b) revealed that the emerging synaptic loss cannot be effectively counterbalanced at high copper concentrations, and c) established the basis for in-depth perusal of molecular events underlying synaptic processes, collectively linked to preventive medical nanotechnology in neurodegeneration.

Keywords: catechin, neurons, morphology, connectivity, copper

Introduction

Over the past two decades, metallotoxins have been implicated in the initiation and progress of neurodegenerative processes [1,2]. Mounting evidence suggests that metallotoxins induced oxidative stress plays a pivotal role in the development of amyloid peptide [3,4] and hyperphosphorylated tau pathologoanatomical features of AD [5]. Prominent among agents inducing

oxidative stress are redox active metals such as Cu(II) [6]. Specifically, Cu(II) have been linked to numerous pathological disorders [7] and associated with the onset of neurological diseases such as AD [8].

AD is the most common age-related neurodegenerative disorder whose pathological hallmarks include mainly senile plaques and neurofibrillary tangles [9,10]. The majority of AD cases (>90%) are idiopathic, with a range of endogenous (genetic-metabolic) and exogenous (environmental-lifestyle) risk factors involved in AD pathogenesis [11,12]. AD affects many people aged 65 years or older, with nearly half of those of age 85 afflicted with this disorder, contributing to 60-70% of dementia cases [13]. Despite persistent research into AD pathogenesis, no cure has been found.

Flavonoids are natural polyphenolics, possessing (metal)antioxidant properties [14] with wide beneficial effects on human health [15-17]. However, there are natural polyphenol agents, which may be exploited for their antioxidant activity against metal ionic reactivity. For instance, Ct can act as an effective anti-oxidant agent, able to improve learning and memory ability [18,19].

To date, little is known at the cellular level about the effects of flavonoids against bioavailable Cu(II). Developing and using advanced flavonoid antioxidant forms, exemplified through encapsulation in silica (SiO_2) NPs, offers a) advantages of mechanical stability and low toxicity for the encapsulated flavonoid, b) prevents flavonoid degradation, and c) improves the pharmacokinetic optimization and controls its biodistribution in the body [20], collectively leading to the efficient permeation of more effective antioxidants through the blood brain barrier toward sensitive brain loci [21].

In the current study, we were poised to a) synthesize the base-catalyzed SiO_2 gel matrices modified with i) PEG 3000, and ii) CTAB cationic surfacta nt was pursued and achieved, b) compare and evaluate the suitability of these matrices, as potential host-carrier materials for the controlled release of the Ct antioxidant flavonoid, and c) investigate of the cytotoxicity and potential protective effects of the Ct-loaded NPs was undertaken under oxidative stress conditions in the presence of Cu(II), notable for its influence on neurodegeneration, in *in vitro* primary hippocampal cell cultures.

Methods

The implementation of the current study was carried out in two phases exploiting chemical as well as biological approaches. The NPs were a) prepared by using sol-gel technique and b) used in the formation of nanocomposites with Ct. During sol-gel synthesis of SiO_2 spheres, equal mass quantities of PEG 3000 and CTAB were added to silica sols, respectively, in order to optimize SiO_2 matrices [22]. Upon optimization, Ct amounts of 0.25, 0.50 and 0.75 g were added for encapsulation SiO_2 sols. To fully characterize the novel nanomaterials, elemental analysis, particle size, z-potential, FT-IR, BET, TGA, and SEM were employed. The outcome of release studies of the loaded Ct from SiO_2 nanoparticles using UV-Visible spectroscopy was necessary for further biological study. To demonstrate the protective effects of Ct NPs against Cu(II), Laser Scanning Confocal Microscopy, Sprague-Dawley hippocampal cell cultures and Immuno (histo) chemistry methods were applied. Cell survival and morphological changes were assessed usingFluorescein isothiocyanate filter for Calcein-AM, Rodamine for PI and Tubulin Tracker cell staining. The workflow of the current study is presented below (Figure 1).

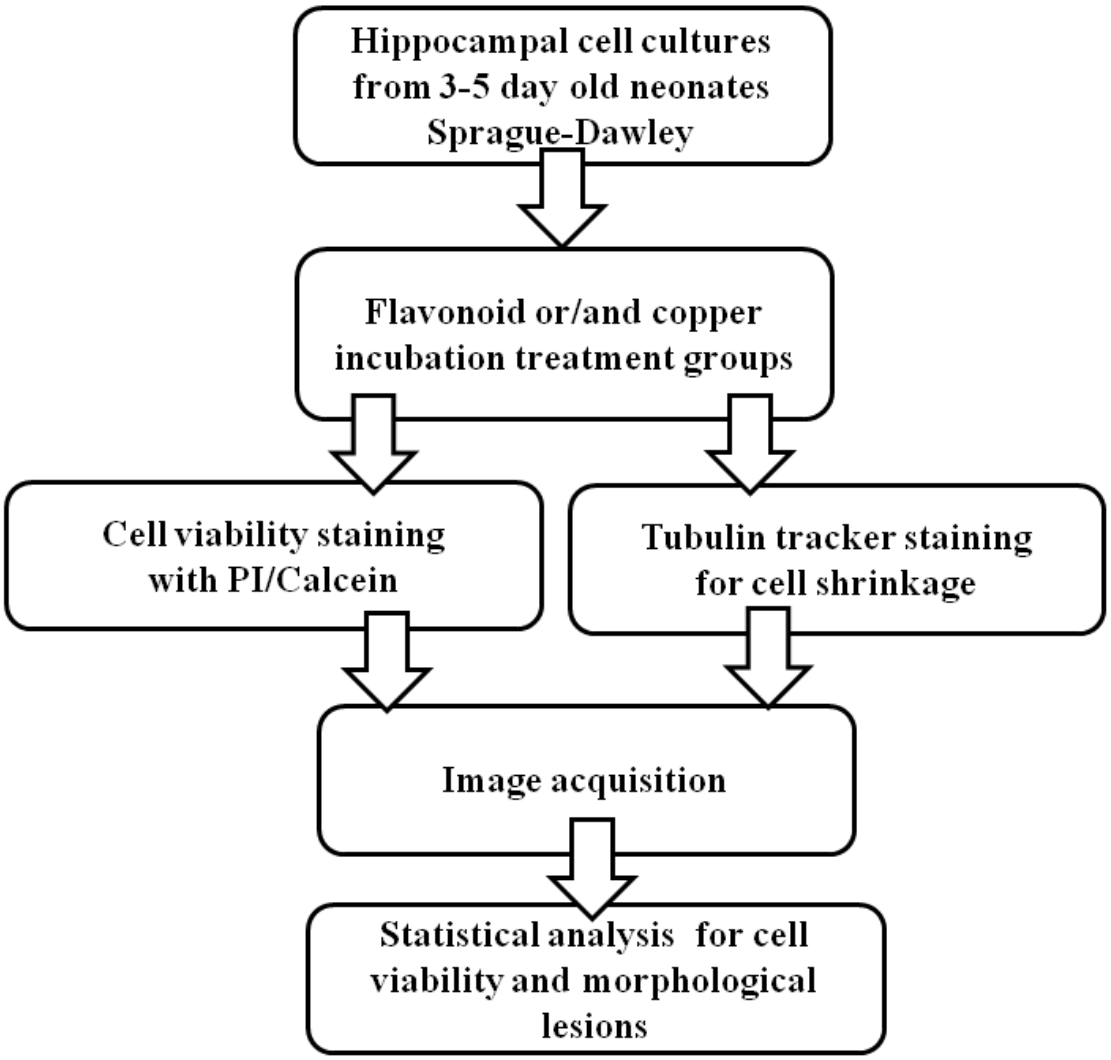

Figure 1. A step-by-step experimental workflow applied in the biological approach of the study.

Furthermore, the potential of the new encapsulated Ct NPs as neuroprotective agents was investigated using primary hippocampal cells and explored against Cu(II)-induced neurodegenerative processes such as shrinkage and cell death. Of note, only the lowest Ct-loaded PEG- and CTAB-modified silica NPs of 0.25 g were employed in this stage of the experiment as the biological investigation was mainly focused on the biological activity of Ct loaded in the NPs. The silica PEG and CTAB-modified NPs applied alone to the cells were found non toxic. Furthermore, the form of Cu(II) used, herein, was copper glycinate at the concentrations of 10, 50 and 100 μM. In addition, three concentrations of Ct-PEG and Ct-CTAB SiO_2 NPs (5, 25 and 50 μM) were selected to study latent protective properties of Ct against Cu(II) in the hippocampal milieu. Initial 24 h incubation time was applied for Ct NPs (alone or in combination with Cu(II)) followed by 3 h of Cu(II). Under sterile conditions, triplicates for each experimental group condition) were used throughout. Statistics were calculated using GraphPad Prism® (Version 5; GraphPad Software, San Diego, CA, USA). Mean absolute survival or shrinkage rates and SEMs were calculated for each condition as well as cell type as previously described in Nday et al, 2010. Furthermore, one way in addition to two way statistical analysis of variance (ANOVA) were applied for within and between-condition comparisons, respectively, followed by post hoc analyses (Tukey). The emerging P values were presented as significant ($P<0.05$) or non-significant (ns). Degrees of significance were recorded as $P<0.05$*

(significant), P<0.01** (highly significant) and P<0.001*** (extremely significant).

Results

FT-IR depiction enhances the differential patterns between PEG and CTAB surface tailored NPs, in that way distinguishing their physical as well as their chemical unique characteristics related to their potential biological behaviour. While the Thermogravimetric analysis was employed for further determination of the properties of the Ct-loaded surface-modified SiO_2 nanomaterials. Moreover, surface morphology observation of the novel Ct surface-modified SiO_2 NPs was carried out using SEM techniques. Furthermore, the variable profiles of surface area as well as pore size recorded in PEG- and CTAB- surface modified SiO_2 NPs using BET analysis emphasize their differential binding properties due to their different chemical and physical characteristics. Specifically, PEG chains insure its expedient entrance into mesoporous channels in and out of the surface matrix of SiO_2 NPs [23], proving its strong interference in the silica polycondensation reaction [24]. The mean particle size and zeta-potential were in line with scanning electron microscopy results. The entrapment efficiency findings on Ct-loaded PEG surface modified NPs were of 60.2%, 63.3% as well as 71.2% which corresponded to the diverse amounts of the Ct encapsulated in the nanomaterials (0.25, 0.50, 0.75 g). Additionally, Ct-loaded CTAB-modified SiO_2 NPs showed 23.8%, 27.9% and 31.7% entrapment efficiency for 0.25, 0.50, 0.75 g, respectively. As a result, the determination of the loading capacity of the SiO_2 matrices was in line with the employed Ct amounts during NPs synthesis. The drug release investigation aimed to assess the pharmacokinetic properties of the novel Ct encapsulated surface modified SiO_2 NPs which turned out to be 75.0%, 79.6%, and 94.3% and 40.3%, 50.8%, and 66.9%, of Ct rate from the Ct-loaded PEG- and CTAB-modified silica NPs (0.25, 0.50, 0.75 g) respectively.

Furthermore, a representative biological activity profile of Ct NPs against copper at specific concentrations used in the current study is summarized in the table below.

Table 1. *Representative biological anti-oxidative activity patterns of Ct nanomaterials against copper glycinate induced cell toxicity*

x	5 μM Ct NPs	25 μM Ct NPs	50 μM Ct NPs
10 μM CuGly	ns	-	-
50 μM CuGly	-	ns	-
100 μM CuGly	-	-	***

CuGly = Copper (Cu(II)) glycinate; Ct NPs = Ct-PEG and Ct-CTAB SiO_2 NPs; - = no co-application needed upon pilot experiments; ns = non significant.

Upon the co-application of Ct NPs and Cu(II), the concentrations of 5 and 25 μM of Ct-PEG or Ct-

CTAB SiO_2 NPs were all protective against Cu(II) into the cell culture. The concentration of 50 μM Ct-PEG or Ct-CTAB modified silica NPs was not able to protect the cells against the highest of Cu(II). The outcome of cell survival profile of all treatment groups employed, herein, was in line with the morphological lesions patterns occurred into the cells due to Cu(II) mediated toxicity.

Conclusions

Overall, the findings suggest that the new hybrid nanomaterials contribute to the improvement of therapeutic activity, better protection against degradation, optimization in pharmacokinetics, better control of bio-distribution, and decrease of cytotoxicity as a consequence of a slower, more stable catechin release rate, thereby counteracting in a dose-dependent Cu(II)-induced oxidative stress and neurodegeneration.

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How Children aged 9-11 years old can communicate with their grandparents

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Abstract

This opinion paper outlines how children aged between nine and eleven years old, can communicate with their grandparents through visual arts and, especially, images. The project was implemented in Cyprus, and the participants were six prepubescent children with grandfathers that suffered from dementia. This study aims to illuminate three aspects. Firstly, to emphasize on the role that fairytales play in human psychology, secondly, to indicate the way through which storytelling can affect human relationships and lastly, to define storytelling as a method of psychoanalysis. Three criteria were considered for the choice of the young participants: a) prepubescent age, b) all participants were related to grandfathers with dementia and c) all participants appeared concerned whether their demented relatives would be able to recognize them. Prepubescent participants used a number of painting materials in order to depict what they had previously experienced in their daily moments with their demented relatives. Later, a discussion took place about the specific experienced moments that, eventually, led - with the support of a coordinator - to the writing of a fairytale consisting of the formentioned stories previously narrated by all the young participants. In this operation all paintings and images were included. By the end of the particular operation, children seemed to acknowledge that the method used helped them to realise and understand that dementia is not so much a personal matter, but that it also affects social and family environment as well. They also claimed to have recognised the importance of visual arts interaction as it is a way of endorsing the ability of personal expression and creativity. Concluding, all young participants appeared in agreement with the fact that the procedure of communication with their demented relatives through visual art was quite constructive as it provided a strong means of communing in a more effective way the feelings between grandchildren and their grandparents.

Key words: fairytales, dementia, grandparents, grandchildren

Introduction

<And I speak to you in fables and parables because this is the way they sound sweeter, and what travesty can't spoken, because it's alive, because it's unspoken, and it proceeds…> George Seferis [1].

While reading a fairy tale to our child and looking through its pictures, we cannot sense the number of symbolic and figurative images and messages that are drawn to its mind. Notions as right

or wrong, guilty or innocent, or even identifications of creatures and animals as good or bad create concepts, stereotypes and maybe, distorted images. Lately, there has been a great effort of upgrading the content of fairytales. Narrations have become interactive and at certain times, more realistic. In every case, though, it is essential we keep in mind that each story or image either drawn on a piece of paper, or shown on television, hides multiple meanings that are conceived by each child according to their comprehensive competence, thus shaping a series of reactions and sensations as we mention in this opinion paper.

Literature Review

It is a fact that, due to socioeconomic changes, intergenerational relationships change day by day. The dual relationship between young people and their parents seem to have become more complicated compared to those of the past. So, there comes a time for almost every individual that has to cope with a three-dimensional role: An individual may have a three part responsibility opposite his own children, his grandchildren and last but not least, his own parents. As previously indicated, what makes a great difference in today's world is the efficacy and duration of the intergenerational relationships [2]. Contemporary postmodern families follow a process of reciprocating between their ascending and descending members. The help and support provided is intergenerational, endogenous and mutual [3]. The new type of family that has been formed as well as its concentration on close relatives, is not always the same, neither does it concern all social categories [4]. The categories that are mainly affected are metropolitan families, youth and the elderly, as opposed to other types such as countrified families. As follows, the contemporary postmodern type of family is utterly connected to contemporary social and demographic progresses [5,6]. As Winnicott might likely say, there is a neutral transitive field in our conscience emerging through the reading of fairy tales and stands in between imagination and reality. Impulsive emotional experimentations may occur to the individual’s imagination, as it is a field freed from the threat of disciplinary borders or persiflage that could ascend from potential unfavorable or fantastic scenarios accordingly. Thus, a child is free to think and act, but mostly connect with its narrator and “play” as wanted in his own story [7]. Also Jung reported that through the safe environment that fairytales provide, children can become aware of the “archetypes” that carry unconsciously. An evil witch or a fearful dragon is most likely connected with an oppressive mother and an emasculating father, accordingly. Likewise, Freud’s long-term discussion supported that unconscious emotions are utterly related to feelings shaped from the ascendancies that come through storytelling, religion, shapes and objects [8]. Besides, Freud’s passionate collection of antiquities confirms his own theory as he maintained a serious number of statuettes that he considered associated with his inner self. Emotional experience is a composition of emotions and meanings. What makes us who we are is our emotions and the way we confront them. To be aware of our feelings means to exist. And in order to trust our emotions we have to experience them with wisdom and mindfulness [9]

As Gerson quotes,

"... our reaction to a family system can travel through a number of channels" [10].

Psychoanalysis' immense contribution to this field lies upon its attempt to penetrate "the visible surface" of imagination, to look "further" and "deeper" and prove that our dreams, like narrations, mean a different thing than what we usually say [11]. Hans Dieckmann embraced firmly the idea that quite an effective way in adult's psychotherapy is for the individual to narrate his/ her favorite fairytale, thus helping them overcome several of their psychological problems [12]. According to this theory, one's favorite fairytale is impressed to memory not randomly but due to the psychological value they tend to give it, always in reference to their own experiences and concerns. Once we realize the deep meaning of a story, we become more capable of deciphering our unconscious thoughts and fears and finally confront them. As implied by the well-known Swedish director, Ingmar Bergman, a fairytale may breed imaginary situations seldom related to reality, however, it builds a road to it, whereas, lies avoid it. Children through fairytales are offered the knowledge of life and are better prepared to adjust to an imperfect adult's society full of unconscious emotional conflicts [13]. According to Bettelheim, fairy tales' greatest importance on individuals at their stage of development is not found in the behavioural education, that is lavishly provided through religion, myths and legends. Fairytales do not describe the world we live in, nor do they give advice on how one should act and behave [14]. Yet, fairytales' therapeutic method occurs as the patient reaches his own conclusions considering its implications and meanings that apply to his personal experiences and inner conflicts [15]. The content of the story chosen each time has nothing to do with the apparent life of the patient but with his inner matters which seem bewildering and so insoluble [16]. Fairytales are not clearly related to the outer world, even though they usually adopt realistic scenarios. The non-realistic aspect of these stories is of huge importance as it clarifies that the powerful function of fairytales is not the fact that they provide a realistic picture of the world, but the inner processes that the individual confronts through reading those stories [17]. Bettelheim considers myths and fairytales to be quite similar. Nevertheless, more often in myths than fairytales, characters are presented as model figures appropriate enough to be imitated by the readers [18]. Myths, like fairytales do, might present an inner conflict and at sometimes may indicate a possible solution, but this does not, necessarily, consist myths' main concern [19]. On the other hand, characters and facts of fairytales also depict inner conflicts, yet they, quite precisely, indicate not only the way of solving them, but they also enlighten a certain behaviour towards individual evolution and development to a higher human beingness [20]. Fairytales are a constant value in our lives. They have always offered a sense of affiliation between family members. Mostly, they build strong relationships between grandparents and their grandchildren creating emotional bonds between distant ages.

Methodology

A fairy tale is a fictional story narrated with the aim to convey several meanings, develop critical thinking skills, teach morals, delimitate human drives and customize behaviors. During this research, the participants were found willing to summon their organizing and supportive skills in order to limit

destruction to its lowest level. Also, children were most likely to empathize with the aggressor when working interactively. In fairytales, children are prompt to identify possible disturbing emotional conflicts that they may be experiencing themselves; however, at the same time fairytales seem to provide them with a generic optimism.

The therapeutic power of fairytale therapy discusses psychological disorders always taking into consideration each child's age. In fact, therapeutic fairytale's merit lies within the ability of viewing the problem through a different perspective, thus providing a shielded way of addressing it. A child's evaluation towards the problem is estimated through the experiential exercises included since the problem is reenacted through participants' art writing and drawings. This particular fairytale therapy was conducted interactively. The story that had been written by one of the children in order to deal with its grandfather's disorder was later on drawn by the children who constituted the team. The fact that the participants were at the same age facing similar problems offered a safe ground for the child to express itself dramatically.

Fairytales are not merely made up for entertainment needs. They are fictional stories with enclosed meanings that need to be conveyed and serve manifold purposes; developing critical thinking and moral values, delimitating human drives and customizing behaviors. Using excess and repetition as mediums, fairytales aim at children's conscience. Ergo, they deliberate daily concerns within the safe environment of literature. Nevertheless, one can't help but wonder what happens when children already face psychological disorders. It seems that fairytales can stand alone as a therapeutic method and there are a great number of psychiatrists, psychotherapists, specialized therapists and teachers who apply fairytale's dynamic to their therapeutic method [21].

Fairytales, fables, myths and legends are imparted down through hundreds of generations. Apart from a cherished means of travelling through tradition, fairytales and stories compose a ductile material always ready to be accustomed to current shapes and serve significant needs. The thrill and pleasure of preschool and school-aged children towards fairytales has often been a subject of research. In child psychotherapy fairytales have been repeatedly used as a therapeutic method. In the research conducted children seemed to have used their acquired organizing and accessory skills in order to delimitate pugnacity. It has also been shown that participants, most of the times when acted interactively, seemed to associate themselves with the bully, or if nothing else, reckon similar feelings. Fairytales used as a therapeutic means helped children decode their own experiences and think about the story in a more coherent way. As readers they appeared to attach themselves to fictional characters portrayed as they reckoned to them similar emotional conflicts and stress. As explained by the specialized art therapist, fairytales can help children understand their inner emotional anarchy and give birth to an overall optimism.

Reading stories with happy endings helps children develop their imagination and comprehension as well as cultivate creative thinking and encourage listening. Fairytales is a unique dialect that maintains its own apparatus. It works in a way that can be well accepted by children due to its multiple narrative methods and the fact that each story is based on fantasy.

In the field of modern pedagogy, fairytales are a fair instrument to prepare children for everyday life. For this purpose, they adapt their language and follow intimately their soul. All human weaknesses and strengths are presented in fantasy contents giving children the opportunity to understand and accept the existence of human problems and manage to cope with interior states and emotions. The innumerable conscious or unconscious images and notions that are arisen to children's mind when reading fictional stories -involving bad wolves, good fairies and dragons- shape consciences, stereotypes and images. A child, at its early age, needs to settle its emotional chaos caused by current surroundings.

Discussion

Fairytale therapy offers children the chance to express their feelings and anxieties. This therapeutic approach operates dually. Firstly, it aims at encountering possible psychosomatic disorders and secondly, it helps the individual become aware of its creative side. Fairytale therapy is being used developmentally, diagnostically, therapeutically and precautionary. It is also proved to have been applied by psychologists, psychiatrist psychotherapists, specialized therapists in child guidance clinics, hospitals and private centers.

The most appropriate age range for effective results of fairytale therapy is considered this of preschool-aged children up to adolescence. Reading fictional stories strengthens our mental development. But reading itself sometimes is not quite adequate considering that young children do not have this ability. The prerequisite is that the child listens to an unsolved story and somehow finds itself attached to it because it acknowledges a similar problem or emotion. Each story has a beginning, middle and end. As a starting point the story cites the problem along with the consequences. However, at the end there is always a solution to the problem. Later on, the child is called to answer comprehensive questions concerning the story or even draw and paint images that had been inspired while reading. In this way, it participates creatively and dramatically to this process [7].

Children who participated in this research were given the chance to choose one out of three fairytales separated in categories. Afterwards, they were called to draw images that had been conceived while reading the stories and answer a questionnaire with both comprehensive and personal context. Craft activities were also involved in most of the fairytale choices. Impressive as it may seem, preschool-aged children seemed to have acted more positively towards their problem after having read the fairytale and drawn pictures.

Dialogues and dialect in fairytales correspond to children's way of thinking always depending on their age; and this has been proved quite helpful as far as it concerns understanding the problem and suggesting a solution as well. Specifically, the narration is initiated by a motive only to reach to the problem and, therefore, proceed to suggesting a solution at the end. According to the principles of art therapy, drawing serves the same purpose. The participant is called to depict the problem that has

preoccupied it beginning from its generic point until the end. To be more precise, a preschooler after having read the fairytale about phobias responded as follows: "*When I talk to my fear it becomes frightened and then goes away…*" Another preschooler participant after having read the fairytale about abuse, actually reported: "*We mustn't hit or disturb others, because we all know it is annoying. We must be gentle with other people*". Quite a memorable experience was that of a pre-adolescent child with a demented grandfather. When asked to draw a picture after having read the relative fairytale he commented upon his own drawing as follows: "*When I visit my grandfather I look like this, but the truth is that I feel much worse*".

The objective of the present project is to establish fairytales as a diagnostic and therapeutic tool and motivate the writing of fairytales with supplementary and up-to-date themes. There has already been a conception of fairytales related to current social or personal issues such as phobias, school bullying and sexual abuse.

Conclusion

In this opionion paper we mention the following: We all live in our own fairytale. Perhaps adults, too, need fairytales in order to live happily ever after. Often, an allegory urges us examine an issue we might be confronting, from another point of view. Fairytales help us view our worries and problems more holistically, philosophically, or even sarcastically. We need to see the problem from all viable aspects, examine it and laugh at it, if we are to solve it. Besides, life's biggest truths are delivered through myths, legends, parables and epics. So, what has to be done in order to deal with our issues? Identify them, give them meaning; adjust to different frames and conditions; and last but not least, speak them sweeter to welcome and accept them".

The author declares that she has no conflict of interests.

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