UC/FPCE_2018

Universidade de Coimbra
Faculdade de Psicologia e de Ciências da Educação

Cognitive function in healthy aging – the effects of cognitive training combined with Transcranial Direct Current Stimulation (tDCS)

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Dissertação de Mestrado em Psicologia, área de especialização em Psicologia Clínica e da Saúde, subárea de especialização em Psicogerontologia Clínica, sob a orientação da Professora Doutora Manuela Vilar.

This work was supported by BIAL Foundation project 2014/495.

Coimbra, 2018

Agradecimentos

Em primeiro lugar, agradecer à Professora Doutora Manuela Vilar. Obrigada pela partilha da sua sabedoria, pela disponibilidade e prontidão, pelo cuidado e minuciosidade, pela dedicação.

Ao ProAction Lab, onde surgiu a oportunidade do primeiro contacto com o mundo da investigação. Faço especial referência ao Professor Doutor Jorge Almeida, que me possibilitou não só a integração neste grupo de trabalho de excelência, como a participação no projeto +Memória, sem o qual esta dissertação não seria possível.

À Lénia Amaral, pelos ensinamentos, pela presença e preocupação, pelo apoio, atenção e ajuda nesta dissertação, mas acima de tudo ao longo de todo o meu percurso neste projeto. Da mesma forma, à Ana Rita Martins, por garantir a minha integração neste projeto, pela partilha de conhecimentos. E à Daniela Valério, por ter sempre uma palavra amiga e me levar sempre numa onda de positivismo.

Aos meus amigos:

Obrigada à Lúcia, a minha eterna companheira, pelo apoio incondicional, pela presença mesmo na ausência, por todas felicidades e infelicidades que me fizeram crescer contigo. Obrigada, Maria João, pela tua forma especial de olhar para o mundo, por me incentivares sempre a não desistir, pelos choros e sorrisos, por te teres tornado numa mulher tão completa e por me completares a mim. Obrigada à Cristiana, por me acompanhares do início ao fim, por seres sempre positiva, por seres sempre divertida, por pensar em ti e só surgirem boas recordações. Obrigada, Bianca Gerardo, por seres o melhor exemplo de que o esforço e dedicação são recompensados, por nunca desistires dos teus objetivos e me incentivares sempre a lutar pelos meus, por me encaminhares sempre no sentido certo. Obrigada, Marisa Lima, o meu "eu" aluado em ponto pequeno, por entrares na minha vida e trazeres esse teu brilho especial. Obrigada por seres sempre feliz e me deixares sempre feliz. Obrigada, Cátia Cabral, por teres sido uma surpresa boa na minha vida, por permaneceres nela e me acompanhares sempe ao longo de todo este percurso, por poder sempre contar contigo.

Obrigada, Madalena, por cresceres comigo, por me acompanhares e deixares que te acompanhe, por teres vivido comigo esta maravilhosa vida que foi Coimbra. Obrigada ao Samuel, o meu irmão não consensualmente adotado. Que continues sempre comigo e me ajudes sempre a levar a vida

com sentido de humor. À distância. Obrigada ao João Chaves, por deixar Coimbra, o meu número de humilhações reduziu abruptamente.

Que saudades. Não podia escolher melhores pessoas para partilhar estes cinco anos.

Obrigada, Leonor, a menina mais doce que Coimbra acolheu, pelo conforto que me trouxeste. Se um dia fui o teu porto de abrigo, hoje és tu o meu.

Obrigada, Amândio, por me conheceres tão bem e, ainda assim, continuares do meu lado, por te lembrares de mim quando me esqueço de tudo, por muitos anos de amizade e pela segurança de tantos mais estarem a caminho.

Obrigada, Luís Pais, pela companhia, pelo apoio, por me fazeres rir nos piores dias, por teres voltado à minha vida com toda essa tua alegria contagiante.

Obrigada, cucas, por me acompanharem ao longo destes cinco anos, por me receberem sempre que regresso a casa e não deixarem que nada mude, por me fazerem sentir saudades de casa. Perdoem-me pela referência especial à minha Jéssica, a minha alma gémea, mamma mia! Muito obrigada pela preocupação, por te lembrares sempre de mim, por rires e sorrires comigo, por trazeres cor aos meus dias cinzentos, que sejamos sempre assim.

Obrigada ao folhado Joaquim, fizeste-me chá quando estava doente e não pediste nada em troca. Aos meus colegas de casa, Joaquim e Bruno, por deixarem as limpezas a meu encargo, decerto a pensar na minha necessidade de exteriorizar a ansiedade. Montarroio não seria o mesmo sem vocês.

Obrigada, também, à madrinha Ângela e ao padrinho Paulo, por estarem sempre presentes e me acompanharem ao longo de todo este crescimento.

Obrigada à madrinha Mariana, pelo carinho e paciência. O meu conhecimento estatístico não seria o mesmo sem ti!

O meu maior agradecimento só pode remeter para a minha família. Pela presença constante, na proximidade e na distância. Por esperarem sempre que regresse a casa e me fazerem querer sempre voltar a casa.

Acima de tudo, muito obrigada ao pai Tino e à mãe Cinda pelo amor e apoio incondicionais, pelo constante incentivo para lutar e alcançar os meus objetivos, por criarem as minhas oportunidades, por se dedicarem ao meu

sucesso tanto quanto eu, por celebrarem as minhas vitórias e não me deixarem ficar pelas derrotas. E à irmã Maria João, o meu laço mais forte, a minha fonte de alegria e eterna melhor amiga.

Por fim, mas certamente não menos importante, deixo o meu maior dos agradecimentos à avó Emília e à tia Graça. A oportunidade de iniciar todo este percurso só se deu com o vosso apoio e, se hoje o concluo, estou certa de que também a vocês o devo. Comecei-o na vossa presença e termino-o com o mesmo sentimento. Vejo-vos no meu céu agora estrelado e não tenho dúvida de que são as minhas estrelinhas mais brilhantes.

“O todo é maior do que a simples soma das suas partes.”
Aristóteles

Funcionamento cognitivo no envelhecimento saudável – efeitos da combinação de treino cognitivo e Estimulação Transcraniana por Corrente Contínua (ETCC)

Resumo

Introdução: O envelhecimento saudável/normativo pode afetar várias funções do domínio cognitivo, como a memória, a atenção, o raciocínio e as funções executivas, ocorrendo esse processo de forma diferenciada em cada sujeito. O aumento da esperança média de vida torna relevante o estudo não só da população idosa, como também das mudanças cerebrais e neuropsicológicas inerentes ao processo de envelhecimento. Surge a necessidade de investigar formas de atenuação e retardamento dos efeitos do envelhecimento na função cognitiva, por forma a manter a capacidade funcional e a autonomia do adulto idoso. Assim, o treino cognitivo (TC) surge como uma estratégia/técnica de restauração, reorganização ou compensação da perda cognitiva, promovendo a manutenção da funcionalidade e o atraso do declínio. Por outro lado, a estimulação elétrica transcraniana (ETCC) emerge enquanto técnica neuromoduladora não invasiva capaz de causar impacto no funcionamento cognitivo. Existem já evidências na literatura de que a sua aplicação pode aumentar os efeitos do TC.

Objetivos: O presente estudo visou avaliar se a aplicação combinada de TC e ETCC produziria efeitos na memória, linguagem, atenção e qualidade de vida considerando adicionalmente a influência da área cerebral estimulada. Procurou-se, ainda, verificar se aqueles se manteriam ao longo do tempo, considerando a presença desses efeitos 4 meses após a intervenção e averiguar as diferenças entre os grupos em estudo.

Metodologia: Foram recrutados 56 adultos idosos saudáveis, distribuídos aleatoriamente por quatro condições: Lista de Espera, *Sham*, com estimulação do Córtex Pré Frontal Dorsolateral Esquerdo (CPFDLE) e com estimulação do Cerebelo. Todos os sujeitos realizaram sessão de *screening* e 3 sessões de avaliação neuropsicológica (*pré* e *pós* intervenção e *follow up*), seguidas de uma ressonância magnética. Os grupos de intervenção (*Sham*, CPFDLE e Cerebelo) receberam/integraram 12 sessões de intervenção, com 20 minutos de ETCC, seguidos de 1 hora de TC. Foi, portanto, analisada a presença de diferenças estatisticamente significativas entre os grupos e nos três tempos de avaliação.

Resultados: Foram obtidos efeitos de interação estatisticamente significativos apenas na qualidade de vida. No entanto, verificaram-se efeitos exclusivos do tempo estatisticamente significativos na maioria das variáveis analisadas.

Conclusões: Ainda que os nossos resultados não sejam conclusivos no que diz respeito à eficácia do protocolo de intervenção, este estudo constitui-se como um importante contributo no ainda longo caminho a percorrer no que diz respeito à reabilitação neurocognitiva e aos processos de avaliação da sua eficácia.

Palavras chave: envelhecimento saudável, funcionamento cognitivo, treino cognitivo, tDCS.

Cognitive function in healthy aging – the effects of cognitive training combined with Transcranial Direct Current Stimulation (tDCS)

Abstract

Introduction: Healthy/normative aging process can affect several domains of cognitive function such as memory, attention, reasoning and executive function, occurring differently in each subject. With the progressive augment of lifespan, becomes relevant the study of not only the elderly population but also of the brain changes that follow this aging process. There comes the need to investigate ways of attenuate and retard the aging effects on cognitive function and maintain the elderly's autonomy. This way, cognitive training (CT) comes up as a strategy/technique of restoring, reorganizing or compensating cognitive losses, promoting the maintenance of functionality and delaying performance decline. On the other hand, transcranial direct current stimulation (tDCS) emerges as a non-invasive neuromodulation technique that can also cause an impact cognitive function. There is literature evidence that the application of active tDCS can enhance the effects of CT.

Objectives: The present study aimed to evaluate if the combined appliance of tDCS and CT produced significant effects on memory, language, attention and quality of life, considering the influence of the stimulated brain area. We also aimed to verify the presence of those effects 4 months after the intervention and ascertained the differences between the different groups.

Methodology: We recruited 56 healthy older adults who were randomly distributed on four conditions: Waiting List, Sham, Dorso Lateral Pre Frontal Cortex (DLPFC) and Cerebellum. All subjects performed 1 screening session and 3 neuropsychological assessments followed by MRI. Intervention groups' subjects (Sham, DLPFC and Cerebellum) received a 12 sessions intervention with 20 minutes of tDCS followed by 1 hour of CT. We analyzed the presence of statistically significant differences between the groups and in the three evaluation moments.

Results: We only obtained statistically significant interaction effects on quality of life. However, we did find statistically significant effects of only time on the majority of our variables.

Conclusions: Even though our results were not conclusive on the efficacy of these intervention protocol, the present study comes as an important contribute to the long road to go in what concerns to neurocognitive rehabilitation and the evaluation of its efficacy.

Key Words: healthy aging, cognitive functioning, cognitive training, tDCS.

Content

Introduction

In the last decade, and as a consequence of the progressive augment of lifespan, several studies have been focusing on the elderly population and specifically on brain aging and its consequences on cognitive function. In fact, it has been proven that the brain can still maintain some of its plasticity, being these subjects able to learn through aging (Silva, 2016a,b).

However, and even in the healthy aging process, there are cognitive changes associated with age. These changes can affect several domains of cognitive function such as memory, attention, language, reasoning and executive function. The grade of these alterations is different in every subject and influenced by a number of variables such as genetic factors, general health, level of instruction, mental activity, humor and personality and social, cultural, racial and ethnic differences (Cancela, 2007).

This way, the active role of the professional has been emphasized over the time as the intervention protocol, program or technique must be defined by the professional and considering the subjects' needs (Silva, 2016b). Concomitantly, cognitive training (CT) emerges as a rehabilitation technique of restoring, reorganizing or compensating those losses. It is a promising way of promoting the maintenance of functionality, which has been proven that despite not canceling cognitive decline, it can delay/slow performance decline (Lemaire, 2016).

Martins, Fregni, Simis, and Almeida (2017), in a literature search, verified as another form of making an impact on cognitive function: the appliance of non-invasive brain stimulation (NIBS) such as transcranial direct current stimulation (tDCS). tDCS is a non-invasive neuromodulation technique that delivers a low electric current to the scalp. In fact, Martin, Liu et al. (2014) in an intra-individual crossover experimental design with healthy right-handed participants, found that subjects who received active tDCS reached overall higher levels of CT than subjects who didn't, suggesting better overall skill acquisition.

Even though there is reported evidence of the efficacy of these techniques, they are still poorly explored and applied in Portugal. There has been a clear investment on the development and validation of neuropsychological assessment instruments but there is still a lack of

literature in what concerns to cognitive intervention and rehabilitation dimensions and their efficacy on our population (see Simões, 2012). This emerges the pertinence of the present study that aims to investigate how the combined application of these two techniques can enhance cognitive function in healthy aging.

The present dissertation is organized in 6 parts: first, it is presented a background, describing the healthy aging process and its inherent cognitive changes, followed by the presentation of CT as a rehabilitation process and tDCS as a way of enhancing the effects of CT, being referred the relevance of the combined application of these two techniques. Posteriorly are presented the objectives of this study, as well the methodology adopted, followed by the results and discussion, which includes integrated analysis of the results, considering the reviewed literature. Finally, the conclusions are presented including the limitations and contributes of the study, as well as its implications on future investigations.

I – Background

a) Healthy aging

It is known that the world's elderly population is fast and uncontrollably growing and the lifespan is quickly increasing. Herewith, there comes the need to augment human cognitive span and to promote the preservation of cognitive function until more advanced ages so that the ability of making informed decisions and living independently is maintained (Chapman et al., 2013).

This way, the term "Successful aging" emerges. Successful aging is, according to Rowe and Kahn (1997), defined in three essential parts and the relationship among them: low probability of disease/disease-related disability; high cognitive and physical function capacity; and active engagement with life. Over the years, this definition has been studied and adapted, considering the several findings on this field (e.g. Baltes & Baltes, 1990; Depp & Jeste, 2006 as cited in Martin et al., 2014). Martin et al. (2014), through a review of literature, have found that the most recent and integrative one considers as main components to a "Successful aging" physical functioning, cognitive functioning, life satisfaction/well-being, social/productive engagement, presence/absence of illness, longevity, self-

rated health, personality, environment/finances and self-rated successful aging. As cognitive function remains as a significant part of successful aging, being consistent over the several approaches, self-perception emerges on the most recent one as a significant factor to the subjects' well-being. This suggests that the subjects' perception of its condition may influence the condition itself.

The "Successful aging" theory is actually consistent with the different models of quality of life (QoL). For example, the "Global Model of Quality of Life" (Felce & Perry, 1993, 1995, as cited in Vilar, Sousa, Firmino, & Simões, 2016), which serves as a foundation to the World Health Organization model (WHOQOL Group, 1995), enhances the role of the subjects' self-perception of well-being, as this well-being evolves both objective and subjective dimensions such as the physical condition, social, material and emotional well-being, personal development and the involvement on significant activities. The similarity of these approaches suggests that a successful aging and quality of life have a direct influence on each other. Additionally, this subjective new dimension, that appears on the most recent definition of "Successful aging", can be seen as a core point of interest when allied to objective measures. However, to consider the individual's self-perception there comes the need to ensure its' cognitive integrity in a way that allows the information obtained to be considered as valid (Vilar et al., 2016).

b) Cognitive changes in healthy aging

As we know, aging is a gradual and inevitable process that occurs differently in each person and is perceived by each person differently. Even in the absence of a diagnosed dementia, evidence shows continuous age-related cognitive declines (Cappell et al., 2010; Cepeda et al., 2001; Kennedy et al., 2009; Mahncke et al., 2006; Mattay et al., 2006, as cited in Chapman et al., 2013) and concomitant brain losses of white matter integrity and functional connectivity, more visible in frontal and temporal networks (Cappell et al. 2010; Hafkemeijer et al. 2012; Kennedy et al. 2009, as cited in Chapman et al., 2013).

Commonly, people over 60 years old report cognitive difficulties, specially in memory (Ávila & de Campos Bottino, 2006). However, brain

modifications associated to the aging process are usually combined with vision and hearing changes and generate alterations on the other main mental/cognitive functions such as language, executive and visuospatial functions, even in the absence of neurological diseases. In fact, older adults need much more time to learn new information, to remember it and even to do everyday tasks (Yassuda, Viel, Lima-Silva, & Albuquerque, 2011).

This aging process and its consequent cognitive changes are highly influenced by different endogenous and exogenous factors. It is known that about 50% of cognitive variability in the elderly may be explained by genetic factors and about 30% of that variability can be explained by their educational level. Besides, healthy elder people who frequently perform mental stimulating activities show better performance in cognitive tests and less longitudinal decline. Additionally, factors as personality and humor do have an influence on cognitive changes. For example, depression is associated to self-perceived insufficiencies and performance deficits in memory tasks. Also, elder people with specialized knowledge about the aging process tend to develop compensatory strategies, that allows them to deal with their cognitive losses, maintaining a high-performance level. In addition, social and cultural environment, cognitive training practice, gender, racial and ethnic differences are also influence factors on cognitive changes due to aging (Cancela, 2007).

Once memory decline is one of the main and first complaints manifested by elder people, especially short-term memory (STM), it becomes extremely important referring that this type of memory is responsible for both maintenance and processing of information and it does suffer from changes caused by the aging process. As people get older, it becomes more difficult to execute mental calculation, problem resolution and the mental organization of the tasks that need to be accomplished (Yassuda et al., 2011).

Besides that, some classes of long term memory (LTM) also reveal changes duo the aging process as it becomes more difficult to codify new information, mainly when it involves retaining details about the physical and temporal context (Yassuda et al., 2011). LTM is divided in two large classes: implicit (non-declarative) memory and explicit (declarative) memory, which includes semantic memory and episodic memory. Implicit memory refers to

procedural memory and the Perceptual Representation System (supporting priming effects and classical and operant conditioning). Explicit memory refers to the conscious process of recalling information, whether it refers to general facts and knowledge (semantic memory) or information about personal experiences and their temporal and spatial contexts (episodic memory) (Tromp, Dufour, Lithfous, Pebavle, & Després, 2015).

Studies show that episodic memory is the most sensitive to the aging process, being the first memory system to show decline both in normal and pathological aging. Once general knowledge and vocabulary are well preserved in normal aging, semantic memory seems to be immune to some of the effects of the aging process. In contrast, episodic memory, whose function is sustained by a vast cerebral network such as the frontal system, parietal cortex, cerebellum, thalamus and the cingulate gyrus, seems to be highly affected by aging (Tromp et al., 2015). Episodic memory performance progressively declines from middle age to old age (Nyberg et al., 2003). Older people experience losses in information processing, which becomes less efficient and both episodic encoding and retrieval processes are impaired. For example, elderly tend to suffer from difficulties in recalling the encoded context and stored information in a detailed way, sometimes exhibiting false recognitions (Tromp et al., 2015).

Regarding to language, elder healthy people tend to use various words in substitution of an adjective or a target noun; to describe the function of the object or its features instead of naming it; and to have difficulties in comprehension and production of complex sentences and organizing their speech. However, this kind of difficulties do not prevent the performance of daily, social and occupational activities (Yassuda et al., 2011).

It is also verified that up to approximately 60 years there is an increase of performance in skills related to the accumulation of past processing (e.g., vocabulary tasks, lexical knowledge, oral production and fluency, general knowledge about the world), associated with semantic memory concepts and crystallized intelligence. However, there is a decrease in performance on tasks that require attentional focus and transformation of information at the moment of the evaluation, associated with tasks of episodic memory and working memory (fluid intelligence) (e.g., general sequential reasoning, induction, quantitative reasoning, speed of reasoning) (Strauss, Sherman, &

Spreen, 2006; Yassuda et al., 2011). In fact, Manard, Carabin, Jaspar, and Collette (2014) consider that these alterations on fluid intelligence (particularly on speed of reasoning) may be on the basis of the decline in proactive control abilities that older adults reveal.

In what concerns to executive function, it is associated to abilities as the formulation of a goal, the planning and the execution of tasks efficiently and the ability to evaluate and correct these actions. For example, in daily tasks, it shows up in actions as estimating time, alternating between tasks, ordinate actions and to control impulses and inadequate actions. In general, healthy elderly do not present significant changes in the essential functions to daily activities and maintenance of autonomy, and only once again there is some slowness and possible use of external aids (such as lists, schedules, alarms) (Yassuda et al., 2011). However, studies have revealed a significant hippocampal shrinkage in people in their mid-50s and an estimated average decline of about 5% of the prefrontal cortex per decade after the age of 20, associated with the degradation of the executive function (Tromp et al., 2015).

As far as visuospatial functions are concerned, they are generally preserved in healthy elderly people who, in the absence of significant visual changes, usually have a good orientation of the physical space, both inside and outside the home (Yassuda et al., 2011).

In what concerns to attentional processes, Lezak, Howieson, Bigler, and Tranel (2012) considered that attention span, similarly to short-term memory and working memory, is a limited capacity. According to McDowd and Birren (1990) older adult's attentional resources are reduced and may influence the execution of cognitive processes. Craik and Byrd (1982) and Mather and Carstensen (2005) considered that age-related changes occurred mainly in situations where attention must be intensively focused, especially in presence of interferences and distractions or when needed a large amount of attentional resources, and due to the need of high degree cognitive control required on those situations. However, attentional processes can refer to several types of attention: 1. attention switching – ability of monitoring two or more stimuli alternately – can be slightly reduced due to generalized decrease of processing-speed (Hartley & Little, 1999); 2. sustained attention – ability of maintaining performance on a task for an extended period –

seems to be relatively well preserved; 3. Selective attention – ability of filtering and focusing on the relevant information from all information given by environment – seems to be affected by aging, being this decline related to the efficiency of inhibitory processes (Zacks & Hasher, 1994).

In addition, the so-called "normal" aging of the brain may be accompanied by mental changes that are superimposable to those found in incipient dementia, leading to differential diagnosis problems (such as in Mild Cognitive Impairment and early stages of dementia, especially Alzheimer's disease). Although neuropsychological, pathological, and consensus neuroimaging criteria are currently established for the differentiation between normal and pathological, brain aging and its alterations continue to raise diagnostic problems in cases of mild cognitive deficits (Damasceno, 1999).

The changes described as characteristic of aging appear as causes of cognitive deficits observed as natural, for example, forgetfulness of recent facts, difficulties of calculation and changes of attention. Many times, the loss itself can only be observed if the patient requires more of his memory than the ordinary, that is, individuals with an established routine, without great need of intellectual activity, tend to detect the loss later (Nordon, Guimarães, Kozonoe, Mancilha, & Neto, 2009).

However, cognitive loss may also be due to other causes, such as stroke, head trauma, metabolic encephalopathy, infection, acute confusion, dementia, alcoholism, hypothyroidism, cancer and even the use of medications (such as anxiolytics, antipsychotics, tricyclic antidepressants, hypnotics, antihistamines, among others) (Nordon et al., 2009).

For example, considering Alzheimer's Disease, it is known as the most common form of dementia and affects both cognitive (specially memory and executive functions) and behavioral domains (Cavallo, Zanalda, Johnston, Bonansea, & Angilletta, 2016). Initially it causes alterations mainly on memory domain, evolving to other cognitive functions such as language, visuospatial abilities and executive functions, leading progressively to total dependency (Albuquerque, Esteves, & Cerejeira, 2016). Even though patients with this pathology gradually lose their decision-making ability, World Health Organization's recommendations for cognitive interventions with these patients aims to promote an active role of

the subject in decision-making as well as in participating and defining aims for that intervention (Clare, 2008, as cited in Silva, 2016a). Thus, even in the presence of pathology, cognitive interventions such as cognitive training have proven to have an important role on promoting the patient's wellbeing.

From a healthcare perspective, there is a major concern within the aging population and its higher prevalence of age-related impairment in cognitive function. This highlights the requirement of the development of strategies in attempt to maintain or enhance cognitive functions. There comes the need of a quick, effective and low-cost identification of solutions to delay cognitive decline caused by the aging process (Kueider, Parisi, Gross, & Rebok, 2012).

c) Cognitive Training (CT)

The most that our brain is involved in intellectual activities, the more plasticity it will have and slower will be the process of presenting symptomatologic losses (Nordon et al., 2009). Actually, studies have shown that there is a significant potential to alter trajectories of cognitive decline on healthy aging. However, the definition of the intervention process may become difficult once older population is characterized as diversified and heterogeneous. The way that the aging process affects individuals is related to a group of complex biological, psychological and environmental variables and the interaction between them (Silva, 2016a).

Once cognitive losses are implemented, there comes the need to use a rehabilitative intervention. Rehabilitation is the process that aims to habilitate the patient to function in an adequately and appropriate way. It requires the evolvement of both professional and patient so that the second one achieves the optimum level of functioning (Wilson, 1999). Thus, Skeel and Edwards (2009) define three types of rehabilitation: restoration (restore lost abilities); reorganization (substitution of lost abilities for preserved abilities); and behavioral compensation (use of strategies to augment existent abilities). The type of rehabilitation technique applied must consider the deterioration level as well as the as the aims of that interventional process.

Therefore, CT, as a restoration psychological intervention, aims to improve cognition in subjects with cognitive impairment (Willis et al., 2006). Its programs focus on the process or functions that show impairment

in the target population besides building up remaining capacities and strengths (Belleville et al., 2006). This way, rehabilitation process can involve the use of intern strategies (aiming the optimization of residual functions and/or replacement of impaired functions) and extern strategies (aiming the compensation of lost functions) (Silva, 2016b). It has been defined in four operationalized criteria: 1. repeated practice; 2. focus on tasks with an inherent problem; 3.use of standardized tasks; 4. target specific cognitive domains (Gates & Valenzuela, 2010). In what concerns to evaluating the efficiency of the rehabilitation process, Hampstead et al. (2014, as cited in Silva, 2016a), reached some parameters that can be considered: neuropsychological measures, self-report, external informant and ecological measures.

CT aims to cause cognitive improvement in specific domains, using a restorative or rehearsal-based approach. It has been shown that CT interventions have effective results concerning the enhancement of cognition and daily functions both in healthy and clinical patients (Willis et al., 2006).

Considering healthy adults samples, Willis et al. (2006) showed that cognitive training tasks can improve cognitive function up to 5 years from the beginning of the intervention, causing better performance on specifically trained abilities, when applied to independent, well-functioning subjects. Ball et al. (2002) confirm this conclusion once their results support the effectiveness and durability of cognitive training on target cognitive functions.

When considering a clinical sample, Belleville et al. (2006) showed that CT, including delayed list recall and face-name association tasks, can improve episodic memory tasks when applied to subjects with mild cognitive impairment. Also, referring to patients with "No Alzheimer's Disease", Kueider et al. (2012) found that classical CT tasks improve reaction time, processing speed, working memory, executive function, memory, visual special ability and attention in subjects older than 55 years old. These authors differ two types of CT: computerized (including neuropsychological software programs and videogames) and classical CT, that consist in pen-and-paper exercises. Computerized CT had a positive impact on cognitive performance and visual spatial abilities when using neuropsychological software programs and enhanced reaction time,

processing speed, executive function and global cognition when using videogames. These computerized CT tasks seem to be a good alternative to classical tasks, once they allow the realization of more specific intervention, considering the subject's individual need. Its administration has lower costs and does not demand a face to face intervention. However, older subjects may not feel comfortable performing this type of tasks, once they may not be familiarized with this type of technology. However, as times are changing, in a near future our elder population will be comfortable using computerized techniques, once technology is being more and more used in our daily routine.

One example of a computerized cognitive training platform is COGWEB. COGWEB is an online platform, developed by Portuguese researchers, that allows the implementation of personalized cognitive training programs decided by a professional. Its aim is to address the major needs identified in memory clinic settings and its exercises involve training several cognitive functions. Even though only 66% of the participants had used a computer before, all of them made positive reviews about the platform (Cruz et al., 2013; Cruz et al., 2014).

Another example of computerized cognitive training is RehaCom®. RehaCom® is a computer-based program that includes several exercises of attention, concentration, memory, perception and daily living activities and different levels to each of them, being appropriate to different rehabilitation phases. It allows the patient to do an independent training as it provides all the instructions necessary and monitors the patient's performance giving feedback and selecting the following levels. Also, it is available in several languages and has been considered ecologically valid as its tasks are similar to real life context tasks (HASOMED, 2012).

Although both COGWEB and RehaCom® platforms are available in the Portuguese language, there were found no validation studies for this population.

d) Transcranial Direct Current Stimulation (tDCS)

Transcranial electrical stimulations, including tDCS, are non-invasive brain stimulation (NIBS) techniques that are mostly used for central nervous system excitability's modulation. The tDCS' main mechanism of action is a

subthreshold modulation of neuronal membrane potentials, causing the alter of cortical excitability and activity dependent on the current flow direction through the target neurons (Woods et al., 2016).

These techniques have been tested as approaches to improve or maintain cognitive performance both in healthy (Zimerman & Hummel, 2010) and clinical populations (Demirtas-Tatlidede, Vahabzadeh-Hagh, & Pascual-Leone, 2013). Over time, there have been evidences of favorable motor and cognitive behavioral effects, once these techniques have an influence on behavior by facilitating or inhibiting neural activity (Hummel & Cohen, 2006; Reis, Schambra, Cohen et al., 2009, as cited in Martins et al., 2017).

tDCS technique has been considered as having a promising capacity in the increasing of learning and cognition for the development of enhanced therapeutic interventions (Martin, Liu et al., 2014). There is strong evidence that NIBS techniques can be used to modulate cognitive functioning both in healthy and neurologic and psychiatric disorders (Martins et al., 2017). Literature shows that tDCS induces significant changes in cortical plasticity (Simis et al., 2013, as cited in Martins et al., 2017) and its results are quite favorable in what respects to cognitive function in healthy older adults (Martins et al., 2017).

In what concerns to memory processes, when comparing Sham stimulation and NIBS, literature supports positive results in increasing memory performance (Martins et al., 2017). Anodal tDCS is an active stimulation and Sham is an inactive form of stimulation used to control the placebo effect. However, there might be an influence of the education level on the effects of tDCS, has Berryhill and Jones (2012, cited in Martins et al., 2017) found that this technique was only beneficial in subjects with more education. Besides, the effects of tDCS may be influenced by the location of the stimulation. Although Ross et. al (2011, cited in Martins et al., 2017) found similar results in older and younger adults, the lateralization of the effect showed differences on those two groups, suggesting that the lateralization of processes such as encoding and retrieval may be associated with aging. These investigators found that only tDCS applied over the left regions increased the retrieval process in older adults.

e) Combined appliance of CT and tDCS

One hypothesized method for improving CT's results is its combination with tDCS. This technique enhances synaptic strength in neuronal pathways that are activated by CT, amplifying the effects of training. Behind the link between CT and tDCS is the principle that an "endogenous" activation (CT) and an "exogenous" neuromodulation (tDCS) will facilitate the activation of neuronal networks which sub serve cognitive functions (Elmasry, Loo, & Martin, 2015).

There is preliminary evidence that suggests that tDCS may transfer these effects to non-trained tasks in some domains as working memory, cognitive control, approximate number sense and arithmetic processing (Elmasry et al., 2015).When synaptic interconnections are strengthened by the interaction between cognitive activity (due do CT and tDCS) and training-based reinforcement, further enlargement of the cortical representation within the activated neuronal network will be allowed, therefore promoting generalization to non-trained tasks (Elmasry et al., 2015).

In fact, it has been proved that the simultaneous use tDCS and CT may augment the subjects' performance on cognitive trained tasks in different cognitive functions, both in healthy and clinical samples (Elmasry et al., 2015).

Stephens and Berryhill (2016) designed a study to evaluate if the combination of tDCS and working memory training improves performance on ecologically valid transfer measures administered in participants' homes. They verified that all the participants demonstrated improvement on trained tasks and that tDCS induced greater transfer gains after 1 month without contact. These gains were observed on standard far transfer tasks along with ecologically valid far transfer tasks. Their results highlight the translational value of the use of interventions based on tDCS in healthy older adults when attempting to maintain their cognitive function.

Also considering healthy older adults, Park, Seo, Kim, and Ko (2014) studied the long-term effects of tDCS of the bilateral prefrontal cortex combined with computer-assisted CT on working memory and cognitive function. In their study, there were two groups of participants: anodal and Sham. Both groups completed 10 sessions of computer-assisted CT

combined with tDCS of the bilateral prefrontal cortex. The results demonstrated improvements on the accuracy of verbal working memory task and on the performance on the digit span forward test, having the effect last up to 4 weeks in verbal memory test. This way, the authors concluded that tDCS changes that altered the bilateral prefrontal excitability during computer-assisted CT may be a beneficial influence on age-related cognitive decrement.

When considering a clinical population, Penolazzi et al. (2015) carried out a case study of Alzheimer's disease with the aim of testing the cognitive effects of tDCS. The effects on cognitive performance were evaluated by the computerized tasks and by neuropsychological tests assessing global cognitive function. They found out that whereas the condition that combined transcranial direct current stimulation and cognitive training had little effects on computerized tasks, it induced stability on the patient's global cognitive functions, lasting approximately 3 months and these effects were not achieved with the Sham condition. They concluded that the synergetic use of transcranial direct current stimulation and computerized tasks of cognitive training appeared to slow down the cognitive decline of the patient.

II – Objectives

The present study aims to evaluate if the combined appliance of tDCS and CT produces significant effects on memory, language, attention and quality of life, and if those effects are maintained over the time. For that, the following specific objectives were defined:

1) Evaluate the effects produced by the intervention on memory, attention and quality of life and the influence of the stimulated cerebral area.
2) Verify the presence of those effects 4 months after the intervention.
3) Ascertain the differences between the different groups.

This way, the following hypothesis were created:

H1 : The combined appliance of tDCS and CT improves the ability of memory.

H2 : The combined appliance of tDCS and CT improves the ability of language.

H3 : The combined appliance of tDCS and CT improves the ability of attention.

H4 : The combined appliance of tDCS and CT has a positive impact on quality of life.

H5 : The improvement of the effects produced by the combined appliance of tDCS and CT are maintained up to 4 months.

H6 : The only conditions that present significant improvements are the intervention groups (Cerebellum, DLPFC and Sham).

III - Methodology

The original study "Episodic memory enhancement in aging: the role of cognitive training combined with tDCS in the medial-temporal cortex and cerebellum on episodic memory performance in the elderly" (BIAL project 495/14) aimed to understand whether and how the combination of tDCS with cognitive training (computerized and manual) facilitates verbal episodic memory in older adults, compared with Sham stimulation combined with cognitive training.

The present work is based on a series of selected variables from the mentioned study involving specific abilities such as memory, attention, language and quality of live. The main point is to investigate whether the combination of tDCS and cognitive training produced significant changes on those areas/domains/functions; if those changes are related to the location of tDCS; if they are maintained over the time and if they are due to tDCS and CT intervention or due to the individual application of cognitive training (as it occurs in Sham condition).

To do this, it was conducted a multi-condition, wait-list, randomized, single-blinded with a third blinded rater, and sham controlled study.

a) Participants

All participants were volunteers. From the sixty-two subjects that completed the screening, five participants were excluded: 1 clinical finding; 2 did not want to do Magnetic Resonance Imaging (MRI); 1 had traces of lead (which is not compatible with MRI scanner); and 1 did not want to receive tDCS. From the fifty-seven subjects who completed *pre*-intervention evaluation, 25 were men and 32 were women, between 61 and 79 years old

(M=68.61; SD=4.95) and with 4 to 23 years of schooling (M=12.28; SD=4.79). One participant dropped out after the first neuropsychological assessment and two participants didn't complete the follow-up assessment (one didn't want to repeat MRI and another didn't attend). This way, for statistical analysis we considered the 56 subjects who completed *pre* and *post* intervention evaluation sessions and the 54 subjects who completed *pre*, *post* and follow up (*fu)* evaluation sessions. The participants were recruited through broad-based advertisements in the community such as flyers, websites, public lectures/talks and in different institutions such as senior universities, community health centers and nursing homes. We used a restricted inclusion criterion, in which subjects needed to be: 1) sixty years old or over (≥60); 2) Portuguese native speakers; 3) right-handed. We also excluded subjects: 1) with history of neuropsychiatric disorders (e.g., stroke, epilepsy, dementia, depression) or head injury; 2) with metallic implants; 3) who intake concurrent medication likely to affect cognition; and 4) had history of alcohol or drug abuse or dependence. Before beginning the study, all participants signed a written informed consent. Each of them where paid 50€ upon completion of the study. This project was approved by the Ethics Committee of the Faculty of Psychology and Educational Sciences of the University of Coimbra and performed following the ethical principles of research with human subjects.

b) Materials

1) Neuropsychological Assessment

Neuropsychological assessment was applied in three moments: before (*pre*), immediately after (*post*) and 4 months after the intervention (*fu*). The protocol for the neuropsychological assessment is outlined below:

Cognitive/Intellectual Global Assessment:

Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005; port. version, Freitas, Simões, Alves, & Santana, 2011; Simões et al., 2008): a cognitive screening instrument which evaluates executive functions, visuospatial capacity, memory, attention, concentration and working memory, language and temporal and spacial orientation. It can reach a maximum score of 30 points, being the higher the better cognitive performance.

Emotional Functioning:

Geriatric Depression Scale (GDS-30; Yesavage et al., 1983; port. version, Simões, Prieto, Pinho, & Firmino, 2015; Simões et al., 2017): a questionnaire developed specifically to evaluate depressive symptomatology in older adults. Consists in 30 items and its scores allow the differentiation of the depressive symptomatology's degree: 0 to 10 points correspond to the absence of depressive symptomatology; 11 to 20 points correspond to mild depressive symptomatology and 21 to 30 points correspond to severe depressive symptomatology.

Functional Assessment:

Adults and Older Adults Functional Assessment Inventory (IAFAI; Sousa, Vilar, Prieto & Simões., 2013; Sousa et al., 2017): consists in 50 items designed to evaluate daily living activities such as basic daily living activities (18 items), householdinstrumental daily living activities (18 items) and advanced instrumental daily living activities (14 items). Higher scores correspond to higher disability. This instrument provides a percentage of the total disability, a total of basic daily living activities disability, household instrumental daily living activities and advanced instrumental daily living disability. Also allows the calculation of percentages related to physical, cognitive and emotional factors/disability.

Cognitive Assessment – Memory:

Subjective Memory Complaints – SMC (Schmand, Jonker, Hooijer, & Lindeboom, 1996; port. version, Ginó, Mendes, Mendonça, & Guerreiro, 2015): an instrument used to characterize memory complaints. Consists in 10 questions which refer to a maximum score of 21 points. Higher scores correspond to more severe memory complaints.

Free and Cued Selective Reminding Test – FCSRT (Buschke, 1984; Grober & Buschke, 1987; port. version, Lemos, Martins, Simões, & Santana, 2012): an instrument of verbal memory and learning. There are 3 rehearsals of free and cued reminding with 20 seconds of an interfering exercise between them. One differed reminding task is applied 30 minutes after. Memory and learning are evaluated by the total of each free and cued reminding rehearsal as well as the total of them.

Continuous Visual Memory Test (CVMT; Larrabee, Trahan, Curtiss, & Levin, 1988; Trahan & Larrabee, 1988): evaluates visual memory ability.

Its application is divided in 3 moments: acquisition (where 112 figures are presented accessing recognition memory by discriminating "new" from "repeated" figures); delayed recognition (applied after a 30 minute delay measuring retrieval from long-term storage by distinguishing "old" figures from perceptually-similar figures) and visual discrimination.

Cognitive Assessment – Attention, Processing speed, Executive Function/Language:

Toulouse-Piéron Cancellation Test (port. version, Amaral, 1967): a cancellation test with an usual 10 minute duration (on the present protocol we used 5 minutes) which evaluates selective and sustained attention. Involves mental control, working memory and processing speed. Provides 3 indexes: work efficiency, dispersion index and total result. Hits and errors can also be measured.

"Symbol Search" (SR) and "Digit Symbol-Coding" (DSC) – Subtests of the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997; port. version, Wechsler, 2008). SR measures information processing speed and visual perception. The total is obtained by the subtraction of the errors to the number of hits. DSC measures speed of processing and executive functioning. Its total is obtained by the total of hits.

Stroop (port. version, Fernandes, 2013): consist in 3 tasks: word reading, color nomination and color of the written word identification (ignoring the words' meaning). Provides a total of each task and allows the measurement of the interference effect.

Verbal Fluency Test (SVF; port. version, Cavaco et al., 2013; Santos, 2009): consist in a semantic fluency test in which the subjects are given one minute to refer the maximum number of words of each category (animals, fruits and vegetables, and actions). Allows the evaluation of processing speed, language production and executive functions. The greater the number of words the better the participants' performance.

Performance validity testing:

Rey 15 – Item Memory Test (Rey 15-IMT; Boone, Salazar, Lu, Warner-Chacon & Razani, 2002; Rey, 1964; port. studies see Vilar et al., 2017): used as a measure of the subjects' effort/motivation. Consists in a single stimulus card with 15 interrelated items that are presented to the participant. Participant is given 10 seconds to memorize the stimulus card

and then is asked to reproduce it. A second task relies on recognizing the 15 previously presented on a set of 30 items. Allows the calculation of the immediate evocations' total (number of hits on the first task) and the combined total. Total combined score is given by the sum of the immediate evocations' total and the second tasks' hits/recognized items minus false positives. Higher results are associated to higher levels of motivation/effort to the task.

Quality of Life:

World Health Organization Quality of Life-Older Adults Module – WHOQOL-OLD; Power, Quinn, Schmidt, & WHOQOL-Old Group, 2005; port. version, Vilar, Sousa, & Simões, 2015; Vilar, Sousa & Simões, 2016): the Portuguese version evaluates 7 dimensions of quality of life: sensory functioning; autonomy; passed, present and futures activities; social participation; death and dying; intimacy; and family/family life (a new/cultural relevant facet). Provides a score to each facet and a total score in which the higher scores correspond to a higher perceived quality of life.

On the *post* intervention assessment, alternative available versions of MoCA and FCRST were used, to avoid learning effects.

The present study does not analyze the totality of the referred protocol. Due to another study being parallelly developed and according to aims of the present study FCRST, Toulouse-Piéron Cancellation Test, and STROOP were not analyzed. IAFAI and GDS were used for inclusion/exclusion criteria purposes only.

The following instruments and respective parameters were analyzed:

Memory: MoCA's parameter "Deferred evocation" and total result; CVMT and SMC total results.

Attention: DSC and SR total results.

Language: SFV's categories: animals, fruits and vegetables, actions and total results.

Performance validity testing: Rey 15 – IMT (combined result).

Quality of life: WHOQOL-OLD (total 28-item).

2) Cognitive Training (CT)

Cognitive training occurred in 12 sessions of 1h each, alternating between computer-based and pen-and-paper CT. For computer-based CT we used RehaCom® cognitive rehabilitation software (HASOMED, 2012) which involved the use of their specific keyboard. This part of the intervention was based on exercises training memory of words (word list learning and retrieval) and memory of faces (face recalling, face-name association). In what concerns to pen-and-paper CT, we used memory exercises that included verbal fluency (categories: foods; animals, clothing, actions, non-eatable vegetables, wild animals, processed foods, objects, birds and occupations), word list learning and retrieval (grocery list), famous faces recognition, memory techniques learning (vanishing cues, spaced retrieval), immediate stimuli retrieval, delayed stimuli retrieval and recognition.

3) Transcranial Direct Current Stimulation (tDCS)

The tDCS intervention required a TCT Stimulator Model 101 (Research Limited, Hong Kong, China), rubber electrodes (5 x 5 cm, 25cm2), sponges (which were soaked in a saline solution), straps with Velcro and measuring tape to locate the stimulating areas.

c) Procedures

The eligibility of the participants was first checked on a screening performed by phone and in-person before the beginning of the study. Eligible participants were randomly assigned (1:1:1:1) to the following groups: 1) anodal tDCS to the left DLPFC plus cognitive training; 2) anodal tDCS to the right cerebellum plus cognitive training; 3) Sham tDCS plus cognitive training; 4) Waiting List group. Participants placed on the first three conditions were not told if they were receiving active or Sham tDCS stimulation. The protocol involved 15 sessions: baseline assessment, 12 stimulation sessions, *post* intervention assessment and 4-month follow-up. On the first session, an informative leaflet and an explanation of the sessions was given to the participants. Assessment sessions included a neuropsychological assessment protocol, carried out by an external blinded rater, and MRI (not considered in the present study). The stimulation sessions were conducted on consecutive weekdays, at the same schedule, and comprised 20 minutes of tDCS, followed by 1 hour of computer-based

or pen-and-paper CT tasks. The investigator providing tDCS was never the same that applied cognitive training, so that both participant and investigator administering the cognitive training were blinded to the experimental condition and that only the investigator applying tDCS was aware of the participants' allocation per group. After completing the 12 intervention sessions, participants were asked to guess whether they received active or Sham tDCS. Participants were only unblinded to their condition after the finishing of the study, after the follow-up session.

1) Cognitive Training (CT)

Cognitive training program focused on memory training and consisted on 6 sessions per modality (computerized or pen-and-paper training). These sessions were administrated in alternate order, so that the sessions' dynamic and the participants' interest were increased.

Computerized exercises consisted on specific tasks of the RehaCom® (HASOMED, 2012) cognitive rehabilitation software (memory for words and memory for faces). Considering pen-and-paper training, the tasks were adapter from a memory training program (Silva, 2016a; Silva, Pinho, Macedo, & Moulin, 2017) and involved the following domains: autobiographical memory, attention, semantic memory, verbal and visual episodic memory.

2) Transcranial Direct Current Stimulation (tDCS)

Anodal tDCS was applied on the 12 consecutive weekdays of the study, in all experimental sessions. From the mentioned intervention groups, two received active tDCS and one received Sham tDCS. Active tDCS groups received 20 minutes of continuous electric stimulation, with 30 second ramping up and 30 seconds ramping down, at an intensity of 2 mA. The anode electrode was placed either on the left DLPFC, over the T3 location according to the 10-20 EEG international system, or over the right cerebellar cortex, following the set up proposed by Pope and Mial (2012) – 1cm under and 4 cm lateral to the inion. Finally, on the Sham condition, the same montage (either DLPFC or Cerebellum) was employed and Sham tDCS was applied with only 60s of real stimulation. It should be noted that, according to Nitsche and Paulus (2011), less than 3 minutes of tDCS induces no effects on cortical excitability and using 60 seconds of stimulation is a reliable

method of blinding once it causes resembling sensations on the scalp as real tDCS. The reference electrode (cathode) was always applied over the right deltoid muscle. To avoid possible confounding effects that may be induced by two electrodes with opposite polarities, an extra-cephalic reference was used. For all conditions, another and cathode rubber electrodes were placed on a sponge soaked in a saline solution and held in place by cloth straps with velcro. To preserve blinding, the investigator placed the tDCS device behind the participants. Participants were accompanied by an investigator throughout the duration of each sessions which repeatedly monitored the current intensity and impedance. At the end of each tDCS session, a questionnaire was filled out and stimulation sites were checked for side-effects.

d) Statistical Analysis

For the present analyses, IBM SPSS (*Statistical Package for Social Sciences* – version 22.0) was used. There were made descriptive statistics including frequencies, means (M), minimum (Min) and maximum (Max) results and standard deviations (SD), used to characterize the sample in what concerns to gender, age and schooling.

To verify the presence of statistically significant differences between the groups in the three times of evaluation (*pre-post* and *pre-fu*), we applied repeated measures ANOVA, considering as within-subjects factor the time and as between-subjects factor the group. To analyze the significance of the changes caused by the interaction of group and time, paired samples t-tests were applied to the different groups. On the presence of the effect of time only, paired samples t-test were applied to the complete sample.

For Student's t-test, Bonferroni correction was considered (p=0.05/4; p=0.0125).

IV - Results

In what concerns to our sample characterization, the distribution of our subjects between the groups occurred randomly. Our complete sample included subjects from 61 to 79 years old (M=68,61; SD=4,95) who completed between 4 and 23 years of schooling (M=12,28; SD=4,79). Waiting list was the group with higher average results of schooling. Sham

had the lowest average results on schooling and DLPFC had the lower average results on age (Table 1; Annex I for descriptive data concerning tests results).

Table 1 - Sample characterization

Group	Age			Schooling		
	Min	*Max*	M(SD)	Min	Max	M(SD)
Complete sample	61	79	68,61(4.95)	4	23	12,28(4.79)
Waiting List	61	79	69,13(6.64)	7	23	13,20(4,59)
Sham	63	77	69 (4,87)	4	17	10,79(5,38)
DLPFC	61	73	67,71(4,01)	4	19	12,29(5)
Cerebellum	61	79	68,57(6,42)	4	19	12,79(4,32)

Concerning our results, we obtained only one statistically significant interaction between time and group: WHOQOL-OLD (quality of life evaluation) on *pre* to *fu* time (see Table 2). Although not showing significant interactions, we obtained statistically significant effects of time and group on SVF's category "Animals" (Table 2). Variables such as WHOQOL-OLD; CVMT's "Immediate" and "Deferred"; SVF's "animals", "fruits and vegetables", "actions" and "total"; DSC and SR showed statistically significant effects of time only (Table 2).

Table 2 - Comparation of the results of the different functions on *pre*, *post* and follow-up evaluations.

	Pre – Post			*Pre - FU*		
	Time (F)	*Group (F)*	*Time x Group (F)*	*Time* (F)	*Group (F)*	*Time x Group (F)*
WHOQOL-OLD	-	-	-	0.15	2.31	3.08*
MoCA						
Deferred Evocation	0.36	1.87	1.25	0.20	1.25*	1.66
Total	0.94	1.50	0.94	0.07	0.93	1.21
SMC	0.02	1.64	1.63	0.04	1.28	0.13
CVMT						
Immediate	72.03***	0.70	0.47	38.70***	1.37	1.84
Deferred	40.41***	2.13	0.62	9.85**	2.39	0.34
SVF						
Animals	13.56***	2.42	1.3	6.35*	3.18*	0.86
Fruits and vegetables	4.09*	0.75	1.50	0.31	1.06	0.68
Actions	17.93***	1.43	1.00	2.29	1.76	1.00
Total	25.99***	1.56	1.03	2.94	2.30	1.00
DSC	24.59***	1.38	1.39	8.50**	1.85	0.53
SR	7.28**	1.94	0.95	20.90***	1.31	0.78
REY15-IMT	0.63	1.62	0.18	0.17	2.33	0.92

*p<.05; **p<.01; ***p<.001

Considering the interaction of group and time on WHOQOL-OLD we verified no statistically significant changes, although there were some variations on the four groups: a decrease of the medium values on Waiting List and DLPFC and an increase of medium values on Sham and Cerebellum (Table 3).

Table 3 – WHOQOL-OLD (Time x Group Interaction effects).

	Pre	*Post*	*FU*	t	
	M (*SD*)	*M* (*SD*)	M (SD)	*Pre-Post*	*Pre-FU*
WHOQOL-OLD					
Waiting List	111.47 (9.67)	-	110.92 (12.20)	-	t=0.30; p=0.77
Sham	105.57 (9.40)	-	107.62 (11.72)	-	t=-1.21; p=0.25
DLPFC	101.67 (13.50)	-	97.50 (12.49)	-	t=2.23; p=0.04
Cerebellum	108 (14.45)	-	110.43 (16.20)	-	t=-1.50; p=0.16

*consider p<0.0125, Bonferroni's correction.

All the variables showed an increase of the medium values from *pre* to *post* moments (Table 4). However statistically significant effects of time were only verified on CVMT's items "Immediate"(t=-8.61; p<0.0125) and "Deferred" (t=-6,42; p<0.0125), on SVF's categories "animals" (t=-3.65; p<0.0125), "fruits and vegetables" (t=-2.00; p<0.0125), "actions" (t=-4.24; p<0.0125) and "total" (t=-5.09; p<0.0125), on DSC (t=-4.91; p<0.0125) and SR (t=-2.70; p<0.0125). Considering *pre* to *fu* changes, only CVMT's items "Immediate" (t=-6.13; p<0.0125) and "Deferred" (t=-3.19; p<0.0125), DSC (t=-2.95; p<0.0125) and SR (t=-4.60; p<0.0125) showed statistically significant effects of time (presenting an overall increase of the medium values (Table 4).

Table 4 – Time effects results, considering the complete sample.

	Pre	*Post*	*FU*	t	
	M (SD)	*M* (SD)	M (SD)	*Pre-Post*	*Pre-FU*
WHOQOL-OLD	106.74 (12.169)	-	106.52 (14.07)	-	-
CVMT					
Immediate	67.23 (6.39)	74.38 (7.17)	73.33 (8.61)	t=-8.61; p=0.00*	t=-6.13; p=0.00*
Deferred	3.30 (1.52)	4.39 (1.52)	3.98 (1.24)	t=-6.42; p=0.00*	t=-3.19; p=0.00*
SVF					
Animals	17.95 (4.07)	20.52 (6.18)	19.89 (6.47)	t=-3.65; p=0.00*	t=-2.49; p=0.02
Fruits and Vegetables	18.02 (4.53)	19.27 (4.82)	18.36 (5.71)	t=-2.00; p=0.05	t=-0.15; p=0.88
Actions	14.58 (5.34)	17.30 (5.48)	15.84 (6.45)	t=-4.24; p=0.00*	t=-1.20; p=0.14
Total	50.54 (11.90)	57.09 (14.20)	54.09 (16.70)	t=-5.09; p=0.00*	t=-1.69; p=0.10
DSC	43.98 (12.00)	49.27 (14.11)	49.34 (16.60)	t=-4.91; p=0.00*	t=-2.95; p=0.01*
SR	20.26 (6.92)	22.20 (6.22)	23.67 (5.82)	t=-2.70; p=0.01	t=-4.60; p=0.00*

* consider p<0.0125, Bonferroni's correction.

Considering the effects of the variable "group" on CVMT's parameter "Deferred" DLPFC presented higher medium values, followed by Cerebellum, Waiting List and Sham. On SVF's category "Animals, DLPFC was the group that presented the highest medium values, followed by Cerebellum, Sham and Waiting List.

Table 5 – Group effects results, considering the different conditions.

	Time	
	M (*DP*)	Qualitative pattern
CVMT		
Deferred		
Waiting List	12.23 (0.86)	
Sham	9.31 (1.09)	Sham < Waiting List < Cerebellum < DLPFC
DLPFC	12.93 (0.77)	
Cerebellum	12.57 (0.98)	
SVF		
Animals		
Waiting List	52.00 (3.08)	
Sham	54.43 (3.11)	Waiting List < Sham < Cerebellum < DLPFC
DLPFC	64.43 (3.58)	
Cerebellum	64.31 (3.76)	

V – Discussion

The present study examined the efficacy of an intervention combining CT and tDCS, through the comparison of the four conditions (Waiting List, Sham, DLPFC and Cerebellum) on the three times (*pre*, *post* and *fu*).

Concerning the cognitive functions results (memory, language and attention) no statistically significant interaction were observed. This way hypothesis H1, H2 and H3 could not be corroborated.

Even though we did not obtain statistically significant interaction between time and group, SVF's category "animals" showed statistically significant effects of both variables separately (time and group) (see Table 2). Considering the effect of time (see Table 4) we verified an increase of the medium values from *pre* to *post* moments (statistically significant), and from *pre* to *fu* moments (not statistically significant), suggesting an improvement of the language ability and pattern of maintenance of that improvement in time.

Considering the effect of group (see Table 5), we verified an overall increase of the medium values, being DLPFC the condition that obtained the highest results, followed by Cerebellum, Sham and Waiting List. Interestingly, some recent studies have been associating DLPFC to language processing, production and comprehension (Klaus & Schutter, 2018). In fact,

D'Souza and D'Souza (2016) found that DLPFC is associated to language-switching tasks and category-switching tasks when the subjects must produce language but not when they had to only understand language. These findings are in agreement with our results, considering that SVF's exercises only required language producing by the participants, by being asked to refer the maximum number of names belonging in a specific category and in a time limited period. We also expected improvements on Cerebellum condition, once this area has been well established as related to language, specifically to motor speech control, central-auditory functions, speech perception, speech timing, phonological aspects of lexical access and top-down mechanisms (Mariën et al., 2013).

Considering that Sham condition, which did not receive tDCS, also increased its medium values on this category, we could assert that these effects would relate to the exclusive appliance of CT, not being related to the stimulated area of tDCS or to tDCS itself. However, this was a blind condition, meaning that the subjects believed they were receiving active tDCS which could have an impact on these results. We could not measure the effects of the subjects' belief on the results, once we did not have a condition where subjects only received CT.

Regarding the Waiting List condition, we also did not expect an increase of medium results once this group did not receive intervention. However, as SVF's task consists on reciting in one minute the maximum number of names belonging to the referred category, it becomes an easily practiced exercise, even in the absence of guided CT tasks. Besides, the same categories were evaluated on the three different times of evaluation, possibly showing a practice effect. We must also consider that even though Waiting List showed improvements, they were more visible in the intervention conditions (Sham, DLPFC and Cerebellum). This is consistent with the fact that these groups trained this category on CT's task of verbal fluency. Although "Fruits and Vegetables" and "Actions" were also trained during CT sessions, "Animals" category was trained in more sessions. Since Waiting List condition is the control group and shows improvements in the absence on the intervention process, we cannot associate these improvements to the combined appliance of CT and tDCS. Although the subjects were randomly distributed within the four groups, these groups

were not controlled or equivalent in what concerns to age and schooling levels. Waiting List was the group with higher medium levels of schooling that can be associated to better performances. Although these subjects did not receive any kind of intervention (either CT or tDCS were applied to them), we could consider that the fact that these subjects had higher schooling levels could present a greater cognitive reserve that can be enhancing these results (Stern, 2012). Additionally, some of these subjects were recruited in senior universities. Although these subjects were not receiving CT, their formation in senior university presupposes some kind of cognitive activity that may be serving as a stimulus in a spontaneous and alternative way. These effects could not be controlled.

Similarly, most of our measures, such as SVF's categories "Fruits and vegetables", "Actions" and "Total"; CVMT's items "Immediate" and "Deferred", DSC and SR showed a statistically significant effect of time exclusively. Our language measures (SVF's categories previously referred) only showed significant effects of time on *pre* to *post* moments. However, our attentional (SR and DSC) and visual memory measures (CVMT's parameters) showed significant effects on both *pre* to *post* and *pre* to *fu* moments (see Table 2).

Even though we did expect improvements from the *pre* to *post* and from *pre* to *fu*, we expected an influence of the condition on those results. With the exclusive effect of time and the improvements presented by the non-intervention condition (Waiting List) we cannot associate these changes to the intervention (Sham, DLPFC or Cerebellum). This way, we must consider that all three assessments used repeated versions of the tests and occurred in relatively short periods of time (12 days from *pre* to *post* and 4 months from *post* to *fu*). In fact, Collie, Maruff, Darby, and McStephen (2003) refer that practice effects can be verified on the repeated appliance of the same instruments in days, months and even years after the first assessment. We cannot prove that the improvements were due to the intervention process or simply by the repetition of the exercises once we did not apply alternative versions of these instruments.

Although the majority of our statistically significant effects of time did reproduce on *pre* to *fu*, CVMT's both parameters and our attentional measures did show statistically significant effects of time on this last

moment. We could consider that this results as associated to the participants' ability to reproduce the acquired techniques on daily live routine. However, these results were not influenced by the group and cannot be related to the intervention itself. By this, we could interpret that subjects' performances were enhanced by the learning and practice effects inherent to the repeated application of the same measures.

Only WHOQOL-OLD (applied only on *pre* and *fu*), which evaluates quality of life, showed a statistically significant interaction between those two moments, presenting differences from *pre* to *fu* moments and between the four groups. When analyzed individually, these interactions do not come as statistically significant. Although we expected that the improvement of the trained cognitive functions had a positive impact on quality of life, as described on the fourth hypothesis (H4), this effect was not entirely verified.

On Sham and Cerebellum conditions, we did verify and increase of the medium values of self-perceived quality of life. As Irigaray, Schneider and Gomes (2011) found out, the application of a cognitive training involving memory, attention (and executive function) does improve psychological well-being in older adults, that present better self-perceived quality of life after the intervention. This relates to the fact that the improvement of cognitive abilities provides the subjects feelings of self-efficacy, autonomy and maintenance of cognitive functionality. Additionally, cognitive function of the elderly seems to be related to psychological wellbeing, presenting a mutual influence. This way, CT provides the means to delay or compensate cognitive losses, allowing the subject to accept them and adjust the mechanisms adopted to deal with them in a way that does not interfere with their daily activities.

Nevertheless, Waiting List and DLPFC conditions showed a decrease on this dimension. To confirm the direct influence of the intervention on quality of life, we expected that Waiting List group did not present improvements, being the only condition in which the subjects did not receive any kind of intervention. However, DLPFC also present decrease of the medium values on WHOQOL-OLD, proving that the combined appliance of CT and tDCS does not imply a better self-perceived quality of life. Once CT was similar in all intervention conditions, we could consider that the cerebral area of tDCS appliance would be interfering on these results, which of we

did not find any evidence on literature. However, we may consider that this intervention exposes the subjects directly to their difficulties, which they could not be aware of once their daily activities did not require the special use of these abilities. This direct exposition may be promoting the subjects' awareness to their cognitive losses. Additionally, in a global appreciation, regardless groups results pattern, quality of life was only measured on pre-intervention moment and on *fu* moment (four months after the intervention). This period between the intervention and the *fu* evaluation required that the subjects used their learnings on their daily routines. One of the limitations of the studies involving and specifically CT tasks remains on its ecological validity. Although the subjects do improve their cognitive functioning in this type of interventions, they show difficulties on applying their learnings to real life circumstances (Moreau & Conway, 2014; Spooner & Pachana, 2006). Besides, the ambiguity of our results can be related to personal traits and experiences, which were not considered on the present study.

Even in the absence of statistical significance, which does not allow us to associate our results to the intervention process (H5 not confirmed), we obtained overall improvements of the medium values from *pre* to *post* and from *pre* to *fu* moments. Considering our statistical analyses restrictions, we must underline that our sample was reduced in number, having a total of 56 subjects which means only 14 subjects per condition. Additionally, we applied a restricted criterion that only allowed the inclusion of healthy cognitive older adults, which did not present significant losses or declines on cognitive functions and formed a slightly heterogeneous sample. Also, the majority of our subjects had considerable levels of schooling (M=12.28; SD=4.79) starting this study with an already high basis of cognitive function. Thus, our sample was composed by generally active, well succeeded older adults with established routines and involved in several activities that allowed them to have a complete daily schedule. In fact, Stordal, Bosnes, Romuld, and Almkvist (2012) found that 8% of their active older subjects' sample, with ages between 70-85 years old, had higher mean levels of memory tasks performance than middle-aged individuals (50-65 years old), suggesting that an active aging cannot only promote the maintenance of cognitive functioning but also delay the deficits associated to de aging process. This way, healthy older adults with active lifestyles can show minor

degreed changes or even the maintenance of cognitive function until the last part of life, in which may appear a terminal decline on the last years of life (Stordal et al., 2012). Our sample included subjects between the ages of 61 and 79 years old (M=68.61; SD=4.95), ages that according to Stordal et al. (2012) refer to middle-age and early stages of aging and in which active older subjects will not present significant changes from the cognitive point of view.

Our sixth hypothesis predicted that intervention groups presented significant improvements. Even though Sham, DLPFC and Cerebellum conditions presented superior results than Waiting List on SVF's category "Animals", these results were not statistically significant. By this, we could not confirm this hypothesis.

On a final reflection we must consider that our neuropsychological assessment states the problem of its specificity to measure efficacy of the intervention. Also, our subjects may not be generalizing their acquisitions which takes us back to one of the main problems of the CT: its ecological validity. These are actually two of the major challenges of neurocognitive rehabilitation (Silva, 2016a,b).

VI - Conclusions

The present study aimed to examine the efficacy of a combined intervention involving CT and tDCS on cognitive function, specifically on memory, language and attention and its impact on quality of life. The results showed an overall augment of the medium values of the referred cognitive abilities, even though we could not relate them to the applied intervention. Also, we did not have conclusive results on the impact of the intervention improvements on quality of life.

This way, it becomes relevant the reference of the limitations of the present study. One of the limitations relates to the fact that our sample had a reduced number of participants, considering that we had four experimental conditions, having 14 subjects each. Additionally, and even though our restricted criterion aimed to equate our sample in terms of cognitive state of functioning and control the influence of other variables, we ended up having a slightly heterogeneous sample that did not differentiate the subjects of our study. We also have to consider that the subjects' distribution between the

four conditions was random and not specifically aiming the equivalent distribution of the subjects through each condition (concerning age and schooling).

Another of our limitation was related to our difficulty in finding alternative equivalent versions of the neuropsychological assessment instruments. This was one of our biggest challenges once we did not have the means to evaluate the effects of practice vs the effects of the intervention. However, the appliance of the same version of the instrument seems to produce a practice effect up to 4 months interval, once these was verified in all conditions, including Waiting List.

Similarly to other studies, another of the limitations of the present study related to ecological validity. Through the appliance of each exercise, subjects were given tips on how to apply their learnings to real life situations. For example, considering RehaCom's exercise of recalling a list of words, subjects were made aware that they could use the same strategies to memorize a shopping list. However, we did not control the effective appliance of those learnings to daily routine activities and do not have information on that parameter.

Also, it was required that the subjects (except for Waiting List) attended our intervention for 12 days and performed 3 neuropsychological assessment moments. The durability of the whole process required a considerable availability from the subjects, which made the recruitment process difficult. This process was also affected by the need to perform a MRI in each assessment moment and the fact that tDCS involves the appliance of electrical current as it is not a known technique in general community.

In terms of future investigations, it would be important to recruit a higher number of subjects, to embrace more advanced ages and to extend the criterion to mild cognitive impairment to understand the efficacy of this kind of program in already established deficits. We consider that it could be interesting to have a semi-structured interview applied on the different neuropsychological assessment moments that objectified the comprehension of the subjects' perception of the intervention, its results and its ecological validity. In what concerns to the experimental conditions, it would be

interesting to have a condition of only CT, without Sham stimulation which we could not measure the effect off.

One of our future suggestions relies on the exploration and direct comparison of the subjects' performance on CT tasks with the results on their neuropsychological assessments. Once our sample was composed by cognitively differentiated subjects we could be achieving a ceiling effect both on the CT tasks and the neuropsychological evaluations. We also suggest the integration and interpretation of our results on the global projects' matrix (Bial project 495/12: "Episodic memory enhancement in aging: the role of cognitive training combined with tDCS in the medial-temporal cortex and cerebellum on episodic memory performance in the elderly").

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Annexes

Summary of the medium values of all analyzed variables considering the four conditions.

Table 1 - Summary of the medium values of all analyzed variables considering the

	Waiting List								
	Pre			*Post*			*Fu*		
	Min	Max	M (SD)	Min	Max	M (SD)	Min	Max	M (SD)
IAFAI*	0	14,58	2,75 (4,36)	-	-	-	-	-	-
GDS*	0	11	3,40 (3,04)	-	-	-	-	-	-
WHOQOL-OLD	97	128	111,47 (9,67)	-	-	-	96	131	110.92 (12.20)
MoCA									
Deferred Evocation	1	5	2.23 (1.39)	0	5	2.43 (1.45)	0	4	2.23 (1.42)
Total	21	29	25.20 (2.42)	19	29	24.50 (2.90)	21	29	24.54 (2.54)
SMC	2	12	5.40 (2.90)	3	11	5.79 (2.91)	0	11	5.57 (2.74)
CVMT									
Immediate	54	80	67.67 (4.46)	65	86	74.43 (7.37)	41	82	70.46 (10.66)
Deferred	0	6	3.07 (1.58)	1	3	4.23 (1.60)	3	6	4.23 (0.83)
SVF									
Animals	9	21	16.13 (3.85)	8	30	18.36 (6.82)	11	25	18.31 (4.03)
Fruits and vegetables	9	24	16.87 (4.70)	11	26	17.29 (4.81)	9	23	17.23 (4.83)
Actions	6	23	13.60 (5.77)	7	28	15.14 (5.72)	7	26	14.23 (5.54)
Total	25	66	46.60 (12.69)	28	78	50.79 (15.59)	30	72	49.77 (13.05)
DSC	26	75	42.33 (13.41)	23	82	46.07 (17.21)	23	82	48.77 (13.98)
SR	6	28	20.13 (6.37)	9	29	22.71 (5.86)	15	30	24.62 (4.48)
REY15	7	30	24.42 (6.84)	10	30	26.64 (6.74)	18	30	26.15 (4.51)
	Sham								
	Pre			*Post*			*Fu*		
	Min	Max	M (SD)	Min	Max	M (SD)	Min	Max	M (SD)
IAFAI*	0	8.16	1.93 (3.19)	-	-	-	-	-	-
GDS*	2	11	4.71 (2.79)	-	-	-	-	-	-
WHOQOL-OLD	89	120	105.57 (9.40)	-	-	-	89	127	107.62 (11.72)
MoCA									
Deferred Evocation	0	5	2.43 (1.60)	0	4	1.79 (1.31)	0	5	2.38 (1.90)
Total	19	30	21.14 (3.06)	17	29	23 (3.14)	17	30	24.77 (3.47)
SMC	0	15	5.64 (3.93)	1	16	6.50 (3.96)	0	12	5.79 (3.70)
CVMT									
Immediate	55	75	64.71 (4.43)	63	84	72.93 (6.73)	61	92	71.15 (9.08)
Deferred	1	6	2.79 (1.48)	1	5	3.50 (1.51)	1	5	3.15 (1.52)
SVF									
Animals	10	23	17.21 (3.33)	10	29	19 (5.51)	11	27	19.62 (4.82)
Fruits and vegetables	12	25	18.21 (4.46)	7	27	19.93 (4.98)	8	26	19.38 (4.89)
Actions	8	21	12.93 (3.87)	12	30	16.64 (4.65)	10	35	16.38 (7.18)
Total	36	69	48.36	30	78	55.57	30	88	55.38

			(8.98)			(12.70)			(15.11)
DSC	18	54	38.43 (11.58)	24	63	46.21 (11.95)	23	67	47.92 (15.33)
SR	10	28	18 (5.20)	8	28	18.64 (6.51)	8	30	21.08 (6.55)
REY15	10	30	24.18 (6.27)	18	30	24.36 (4.41)	10	30	24.38 (6.74)

DLPFC

	Pre			*Post*			*Fu*		
	Min	Max	M (SD)	Min	Max	M(SD)	Min	Max	M (SD)
IAFAI*	0	6.25	2.87 (2.34)	-	-	-	-	-	-
GDS*	2	20	7.14 (4.67)	-	-	-	-	-	-
WHOQOL-OLD	86	128	101.67 (13.50)	-	-	-	78	119	97.50 (12.49)
MoCA									
Deferred Evocation	0	5	1.93 (1.27)	0	5	2.43 (1.65)	1	4	2.36 (0.84)
Total	20	28	24.36 (2.10)	14	30	25.47 (4.24)	19	27	24.50 (2.14)
SMC	1	16	6.57 (4.31)	2	12	6.50 (3.16)	2	15	6.86 (3.63)
CVMT									
Immediate	57	84	67.71 (6.98)	61	86	75.50 (7.00)	62	91	76.71 (7.21)
Deferred	0	6	3.71 (1.44)	2	6	4.86 (1.17)	3	6	4.36 (1.01)
SVF									
Animals	11	26	19.07 (4.23)	14	36	23.71 (6.51)	12	29	21.64 (5.03)
Fruits and vegetables	10	27	18.79 (4.28)	12	24	18.93 (3.77)	11	28	19.71 (4.07)
Actions	7	26	15.29 (6.18)	8	26	18.71 (4.76)	8	25	16.79 (5.12)
Total	35	78	53.14 (12.89)	37	79	61.36 (12.84)	39	73	58.14 (10.05)
DSC	27	79	49.71 (15.34)	33	73	53.07 (13.30)	36	78	54.14 (12.04)
SR	3	33	23.14 (8.45)	14	32	24.14 (5.75)	16	31	24.71 (5.06)
REY15	21	30	27.73 (3.07)	27	30	29.18 (1.08)	16	30	27.07 (4.71)

Cerebellum

	Pre			*Post*			*Fu*		
	Min	Max	M (SD)	Min	Max	M (SD)	Min	Max	M(SD)
IAFAI*	0	6.12	2.18 (17)	-	-	-	-	-	-
GDS*	0	9	2.64 (2.56)	-	-	-	-	-	-
WHOQOL-OLD	74	138	108 (14.45)	-	-	-	69	137	110.43 (16.20)
MoCA									
Deferred Evocation	0	5	3.00 (1.41)	0	5	3.07 (1.73)	0	5	3.07 (1.39)
Total	21	29	25.50 (2.53)	22	30	25.79 (3.07)	20	29	26.00 (2.83)
SMC	1	8	4.50 (2.18)	1	7	3.71 (1.73)	1	7	4.36 (1.91)
CVMT									
Immediate	58	81	68.79 (6.55)	62	85	74.64 (8.02)	60	85	74.64 (6.50)
Deferred	2	6	3.64 (1.55)	2	6	4.79 (1.53)	2	6	4.14 (1.23)
SVF									
Animals	13	25	19.50 (4.24)	12	27	21.00 (4.85)	10	36	22.92 (6.24)
Fruits and	12	26	18.29	14	32	20.93	1	25	19.85

vegetables			(4.89)			(5.30)	2		(4.30)
Actions	9	25	16.57 (5.00)	10	29	18.71 (6.35)	12	26	18.31 (4.89)
Total	36	74	54.36 (11.99)	41	88	60.64 (14.31)	34	77	61.08 (12.88)
DSC	26	62	45.57 (9.38)	27	82	51.71 (13.56)	34	81	53.43 (14.28)
SR	7	32	19.79 (7.02)	11	33	23.29 (5.88)	15	33	24.14 (6.74)
REY15	12	30	26.09 (5.38)	18	30	27.00 (4.69)	24	30	28.86 (1.88)

*tests only applied on screening for inclusion/exclusion purpose.