Universidade do Minho
Escola de Psicologia

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Working memory and neuroplasticity in older people: A behavioural and neurofunctional approach

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Tese de Doutoramento em Psicologia Básica

Trabalho efetuado sob a orientação da
Professora Doutora Adriana Sampaio
e da
Professora Doutora Sandra Carvalho

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STATEMENT OF INTEGRITY

I hereby declare having conducted this academic work with integrity. I confirm that I have not used plagiarism or any form of undue use of information or falsification of results along the process leading to its elaboration.

I further declare that I have fully acknowledged the Code of Ethical Conduct of the University of Minho.

University of Minho, June 27th, 2019.

Working memory and neuroplasticity in older people: A behavioural and neurofunctional approach

Working memory training (WMT) has been used to promote neuroplasticity in older people and tDCS has been proposed to boost WMT effects. Nevertheless, there is not robust evidence of WMT effectiveness and the few studies assessing the combination of tDCS with WMT used cognitive tasks as endpoints. However, the use of different markers, as the event-related potentials (ERPs), can be useful to better understand the combined or individual effects of these interventions. Thus, the studies presented in this dissertation aimed to assess WMT effects, as well as, the add-on effects of tDCS. Given the need to use different endpoints to measures WMT-induced neuroplasticity, an additional aim was to assess if the ERPs can be used as indexes of fluid intelligence (Gf), a commonly assessed constructed to infer generalization of WMT.

In the first study, we presented a meta-analysis on the effects of WMT in healthy elderly. Small significant and long-lasting gains were observed in working memory (WM), but not in short-term memory (STM) and Gf tasks. Type of training tasks, the adopted outcome measures, the training duration, and the total number of training hours moderated WMT effects. In the second study, we performed a systematic review on the uses of tDCS to boost WM in healthy older adults. The studies suggest that tDCS may modulate WM in this population, improving the accuracy and shortening the reaction time. In the third study, we performed a randomized double-blind controlled experiment to evaluate the effects of 5-day WMT coupled with tDCS in healthy older adults. Fifty-four participants were assigned to one of three groups: 1) WMT (dual *n*-back task)+active tDCS (atDCS); 2) WMT+sham tDCS (stDCS); or 3) sham task + sham tDCS. During the training, both groups that performed the dual *n*-back task (WMT+atDCS; WMT+stDCS) improved throughout sessions, with no significant differences between them. However, the "WMT+atDCS" was the only group that presented gains in Gf and verbal STM after training (i.e., next day after the intervention) and at follow-up (i.e., 15 days follow-up). Finally, in the fourth study, we explored whether ERP components (i.e., P2, P3b and the LPC - late positive complex) are associated with Gf in the elderly. Fifty-seven participants performed a continuous performance task and a visual oddball paradigm while EEG was recorded. They were divided into high-performance (HP) and low-performance (LP) groups according to their performance in the Raven's Advanced Progressive Matrices test (RAPM). HP group presented significant higher LPC amplitudes in the CPT and shorter P3b latencies in the oddball task when compared to the LP group.

Keywords: fluid intelligence; late positive complex; older adults; P3b; tDCS; working memory training.

Memória operatória e neuroplasticidade em adultos em idade avançada: Uma abordagem comportamental e neurofuncional

O treino da memória de trabalho (WMT) tem sido usado para promover neuroplasticidade em idosos e a ETCC tem sido adotada para potencializar seus efeitos. No entanto, não há evidências robustas da eficácia do WMT e os poucos estudos que avaliaram a combinação da ETCC com o WMT usaram tarefas cognitivas como medidas. O uso de diferentes marcadores, como os potenciais evocados (ERPs), pode ser útil para entender melhor os efeitos dessas intervenções. Assim, os estudos desta dissertação objetivaram avaliar os efeitos do WMT, bem como, os efeitos adicionais da ETCC. Dada a necessidade de usar diferentes parâmetros para mensurar a neuroplasticidade induzida pelo WMT, um objetivo adicional foi avaliar se os ERPs procedem como índices de inteligência fluida (Gf), um construto comumente avaliado para inferir generalização do WMT.

No primeiro estudo, apresentamos uma meta-análise sobre os efeitos do WMT em idosos. Foram observados pequenos e duradouros ganhos na memória de trabalho (WM), mas não na memória a curto prazo (STM) e Gf. O tipo de tarefas treinadas, as medidas adotadas e a duração/número total de horas de treino moderaram os efeitos. No segundo estudo, realizamos uma revisão sistemática sobre o uso de ETCC para melhorar a WM em idosos saudáveis. Os estudos sugerem que a ETCC pode modular a WM nessa população, aumentando a precisão e reduzindo o tempo de reação. No terceiro estudo, foi realizado um experimento aleatório duplo-cego para avaliar os efeitos do WMT associados à ETCC. Cinquenta e quatro idosos foram designados para um de três grupos: 1) WMT (tarefa *dual n-back*) + ETCC ativa (aETCC); 2) WMT + sham ETCC (sETCC); ou 3) tarefa placebo + sham ETCC. Durante o treino, os dois grupos que realizaram a tarefa *dual n-back* (WMT+aETCC; WMT+sETCC) melhoram ao longo das sessões, sem diferenças significativas entre eles. No entanto, o "WMT + aETCC" foi o único grupo que apresentou ganhos na Gf e STM após o treino e no seguimento de 15 dias. Por fim, no quarto estudo, exploramos se os componentes dos ERPs (P2, P3b e LPC – *late positive complex*) estão associados à Gf. Cinquenta e sete idosos realizaram uma tarefa de desempenho contínuo (CPT) e um *oddbball* visual enquanto o EEG era gravado. Participantes foram divididos em grupos de alto desempenho (HP) e baixo desempenho (LP) de acordo com seu desempenho na Matrizes Progressivas Avançadas de Raven (RAPM). O grupo HP apresentou amplitudes superiores no LPC evocado pela tarefa CPT e latências mais curtas na P3b evocada pela *oddball* quando comparado com o grupo LP.

Palavras-chave: ETCC; idosos; inteligência fluída; LPC; P3b; treino da memória operatória.

LIST OF ABBREVIATIONS

ANCOVA - Analysis of Covariance

Amp - Amplitude

Aospan - Automated Operation Span Task

atDCS - Active tDCS

AUC - Area under the Curve

AV - Auditory-verbal

BDNF - Brain-derived Neurotrophic Factor

BF - Bayes Factors

BWD - Backward

CACT - Computer-assisted Cognitive Training

CBT - Corsi Block-Tapping Testing

CERAD - Consortium to Establish a Registry for Alzheimer's Disease

CFQ - Cognitive Failures Questionnaire

CI – Confidence Interval

CONSORT - Consolidated Standards of Reporting Trials

CPT - Continuous Performance Task

CWMS - Categorization Working Memory Span

CWIT - Color-word Interference Task

CVLT - California Verbal Learning Test;

DFT - Design Fluency Test

DKEFS - Delis-Kaplan Executive Function System

DLPFC - Dorsolateral Prefrontal Cortex

DS - Digit Span

DSC - Digit Symbol-Coding

EE - Estimate Error

EEG - Electroencephalography

eKFA - electronic Questionnaire for Cognitive Failures in Everyday Life

EPS - Everyday Problem Solving

ER - Evidence Ratio

ERP - Event-related Potential

ETCC - Estimulação transcraniana por Corrente Contínua

FIM - Functional Independence Measure

fMRI - functional Magnetic Resonance Imaging

FU - Follow-up

FWD - Forward

GAI - Geriatric Anxiety Inventory

GDS - Geriatric Depression Scale

Gf - Fluid intelliggence

GLM - Generalized Linear Model

HC - Henmi and Copas

HP - High-performance

IGF-1 - Insulin-like Growth Factor-1

KAB-Icons - Kaufmann Assessment Battery for Children

Lat - Latency

LMMs - Linear Mixed Models

LP - Low-performance

LPC - Late Positive Complex

LPS - Leistungsprüfsystem

LST - Listening Span Test

M - Mean

MMSE - Mini-Mental State Examination

MoCa - Montreal Cognitive Assessment

n.a. - Not Applicable

n.c.- Not Clear

PASAT - Paced Auditory Serial Addition Test

PC - Parietal Cortex

PCA - Principal Component Analyses

PCG - Passive Control Group

PFC - Prefrontal Cortex

PP - Posterior Probability

PPC - Posterior Parietal Cortex

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Rand - Randomized

RAPM – Raven's Advanced Progressive Matrices

RCPM - Raven Colored Progressive Matrices

ROC - Receiver Operating Characteristic

RT - Response Time

RSPM - Raven's Standard Progressive Matrices

RVE - Robust Variance Estimation

SD - Standard Deviation

SDC - Symbol-Digit Coding

SE - Standard Error

stDCS - sham tDCS

STM - Short-Term Memory

TAP - Test of Attentional Performance

tDCS - Transcranial Direct Current Stimulation

TEA - Test of Everyday Attention

TIADL - Timed Instrumental Activities of Daily Living

TMT - Trail Making Test

TOVA - Test of Variables of Attention

VAS - Visual Analogue Scale

VEOG - Vertictal Electrooculograph

VLMT - Verbal Learning Memory Test

VS - Visuospatial

WAIS - Wechsler Adult Intelligence Scale

WM - Working Memory

WMT - Working Memory Training

WMS - Wechsler Memory Scale

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CHAPTER I

INTRODUCTION

Introduction

Ageing Population

The rapid growth in elderly population ageing is a worldwide phenomenon. In 2017, the number of people aged 60 or more was about 962 million, representing 13% of the world population. However, the estimate is that this number will surpass 2 thousand million in 2050, and it will be three times more by the year 2100 (UN, Department of Economic and Social Affairs, & Population Divison, 2017). Figure 1A shows the distribution of world population by age and sex, while Figure 1B shows the life expectancy by region.

As can be seen in Figure 1C, Europe has the world's largest proportion of old people, representing 25% of the total European population. In Portugal, this scenario is not different (see Figure 1D). In 2017, more than 20% of the Portuguese population was aged 65 or over (FFMS, 2018). According to the National Statistical Institute of Portugal, the estimate is that the ageing population will double by the year 2080 (INE, 2017).

Challenges of populational ageing and actions to overcome them

Typical ageing presents a pattern of a general cognitive alterations that may change the daily life of older adults. Whereas cognitive impairment is evident in the domains of WM, Gf, episodic memory, spatial ability, and processing speed, other domains including language abilities and implicit memory seem to be preserved (Bopp & Verhaeghen, 2005; Deary et al., 2009; Park et al., 2002; Salthouse, 1991, 2018; Verhaeghen & Salthouse, 1997). These cognitive changes are concomitant with alterations in brain volume and size, white matter integrity and myelin, dendritic shape and connection; and blood flow. The first age-related brain changes are more evident in the posterior, frontal, and parietal brain areas. Specifically, prefrontal cortex and the striatum are the areas most deteriorated. Degradation in hippocampus is also reported (for a review, see Humayun & Yao, 2019)

Ageing is associated with an increased risk of dementia (Chaves, Santos, Alves, & Salgado Filho, 2015; Pusswald et al., 2015). More specifically, the dementia incidence rate doubles its value every five years after the age of 65 (Corrada, Brookmeyer, Paganini-Hill, Berlau, & Kawas, 2010; Jorm & Jolley, 1998). In Portugal, the prevalence rate of cognitive impairment in people aged between 55 and 79 is

12.3%, whilst the cognitive impairment associated with dementia has a prevalence estimated to be 2.7% (Nunes et al., 2010).

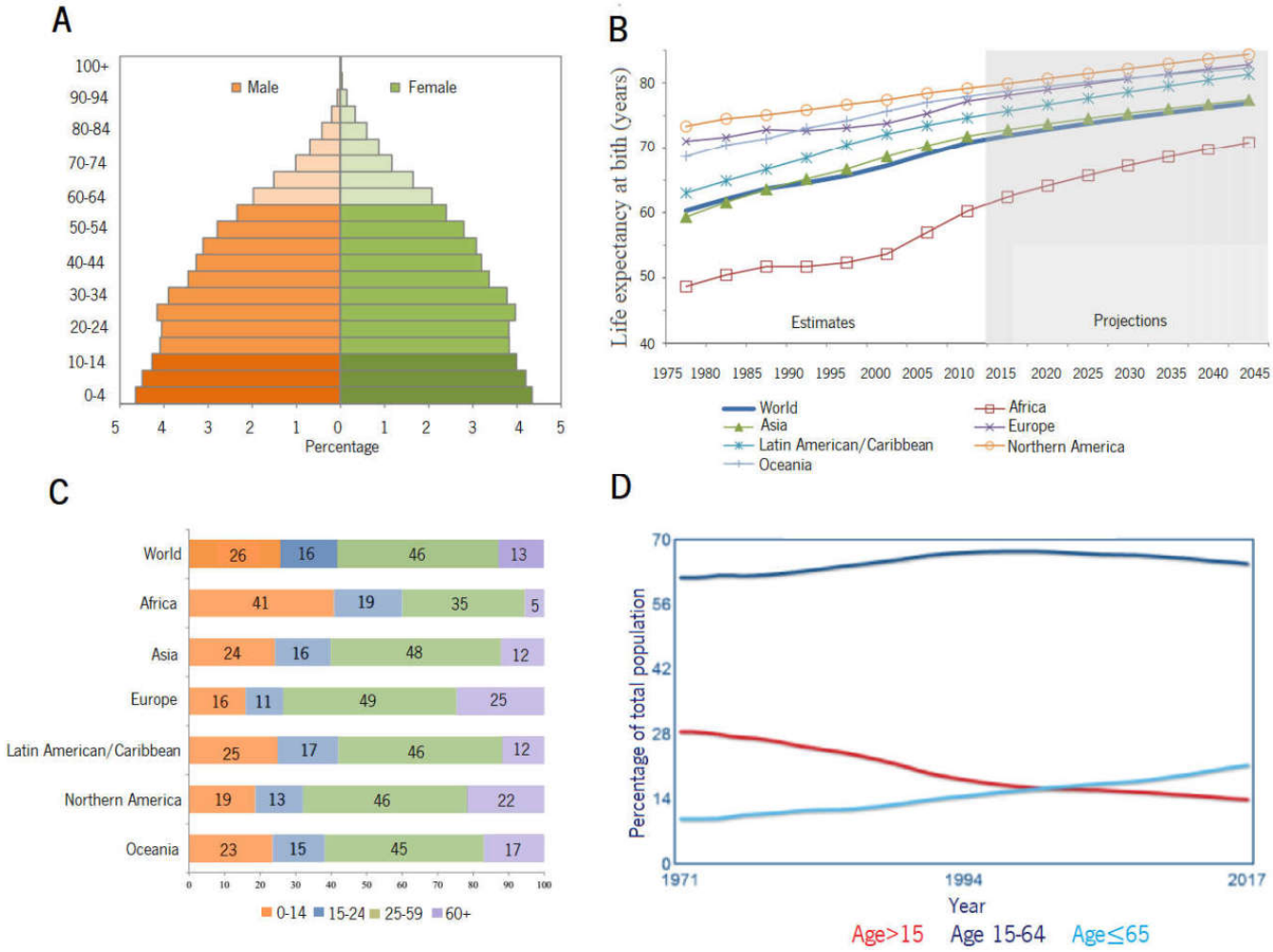

Figure 1. **A.** Distribution of the world's population by age and sex in 2017. **B.** Life expectancy at birth (in years) by region: estimates 1975-2015/ projections: 2015-2050. **C.** Percentage of population in broad age groups in the world and by region, 2017. Reprinted from World Population Prospects: the 2017 Revision (pages 2, 8, and 10), by UN, Department of Economic and Social Affairs, Population Division, 2017, New York: UN. ©(2019) UN. Used with the permission of the UN. **D.** Portuguese population by age group. Red= people aged less than 15; Dark blue= people aged between 15 and 64. Light blue= older people (65 or over). Adapted from Fundação Francisco Manuel dos Santos, Retrato de Portugal PORDATA, 2018 edition, page 9 (based on data from INE, PORDATA). Retrieved from https://www.pordata.pt/ebooks/PT2018v20180713/mobile/index.html. Adapted with permission.

As a consequence, the growth in elderly population is posing various challenges to all sectors of the society with macro and individual implications in many aspects. For example, from a macro perspective, it brings social and financial issues associated with the demographic changes and the imbalance between taxes and pensions; together with an increased financial burden to the government. There is also a great load on health-care systems and caregivers due to the need for specialized goods and services. From an individual perspective, aging may be associated with dependence, isolation, abuse, reduction in physical capability, and change in many aspects of the family structure (Araújo, Paúl, & Martins, 2011; Gil, Kislaya, et al., 2015; Gil, Santos, et al., 2015; Valtorta, Kanaan, Gilbody, Ronzi, & Hanratty, 2016).

Faced with these challenges, a growing interest in preventive actions to help people to live longer with less disability and less functional limitations has been emerging. As a matter of fact, the World Health Organization pointed out that the concept of ageing needs to change so that old age would not be synonymous of dependency (World Health Organization, 2015). Accordingly, initiatives to promote successful ageing emerge in the field of cognitive enhancement, more specifically using cognitive training (Melby-Lervåg, Redick, & Hulme, 2016) or brain stimulation (Hanley & Tales, 2019). On top of that, it is also of paramount importance the study of markers of optimal ageing covering both neurofunctional and behavioural outcomes. These markers would be essential to monitor and evaluate the efficacy of enhancement therapies (Belleville & Bherer, 2012). Moreover, the characterization of typical ageing is fundamental to determine thresholds of misfunctioning in the population that will be important to characterize non-healthy ageing. Otherwise, the identification of abnormal ageing would not be possible (Salthouse, 2018).

In this regard, the next sections will discuss about the cognitive training (focusing especially on the working memory training) and the tDCS, techniques which could be used in the promotion of healthy ageing, as well as about factors that may moderate the effects of these interventions. We will also present one section about the neurophysiological signatures of aging, since it could be used as markers of brain functioning in healthy older people.

Base of cognitive training

Cognitive training is a technique that consists of the practice of structured tasks aiming the improvement or maintenance of cognitive functions (Bahar-Fuchs, Martyr, Goh, Sabates, & Clare, 2019),

increasing cognitive reserve, which is the individual's brain capacity to tolerate insults and pathological processes without showing clinical deficits or symptoms (Papp, Walsh, & Snyder, 2009). Cognitive reserve is related to the people's experiences and behaviors, such as the participation in stimulating activities (Cramer et al., 2011) and is grounded on the concept of neuroplasticity (Hebb, 1949; Ramón Y Cajal, 1906).

Neuroplasticity reflects the structural and functional brain potential to reorganize itself in response to environmental demands (Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010). Neuroplasticity occurs through different processes such as synaptogenesis, apoptosis, and changes in grey and white matter density. The assumption is that cognitive training may drive adaptive changes in the neural system and thus promoting neuroplasticity (Cramer et al., 2011).

Cognitive training studies have shown the potential of this intervention to induce neuroplasticity, namely being associated with alterations in the density of dopamine receptors (e.g., Li et al., 2008; McNab et al., 2009), neural volume (e.g., Boyke, Driemeyer, Gaser, Buchel, & May, 2008), hippocampal mean diffusivity and volume (e.g., Lövdén et al., 2012), brain activation (with mixed results: decrease and increase in activation see Buschkuehl, Jaeggi, & Jonides, 2012, for a review) and resting state functional connectivity (e.g., an increase between the medial prefrontal cortex and precuneus and a decreased functional connectivity between medial prefrontal cortex and the right posterior parietal and lateral prefrontal cortex), and neuroelectrophysiological functioning (e.g.,increasining in P300 amplitude (Pergher, Wittevrongel, Tournoy, Schoenmakers, & Van Hulle, 2018).

The first experiments testing the effects of cognitive training were strategy-based training focusing in mnemonic strategies (e.g., method of loci, which uses visualization techniques to organize the information to be stored) as a way to teach older adults to better perform on episodic memory or Gf tasks (for a review, see Verhaeghen, Marcoen, & Goossens, 1992). However, strategy-based training gains are more pronounced in young adults then in older people, magnifying age-related differences (Neely & Nyberg, 2015). Additionally, although these strategy-based training yield long-lasting task-specific gains, they show limited evidence of transfer effects (Neely & Nyberg, 2015).

In this regard, no clear criteria is set to define transfer distance, however near transfer is normally defined as an improvement on tasks that are similar to the trained task and that share the same mechanisms or components, while far transfer represents an improvement on tasks that measure abilities other than the trained one.

Generalization of cognitive gains to other tasks and cognitive processes is very important since it implies that the cognitive process is actually improved, bringing gains to other domains of functioning which are relevant to maintain autonomy in daily life (Lövdén et al., 2010). Thus, the interest in the process-based training targeting a core process (e.g., working memory) is based on the assumption that by enhancing this domain, all other constructs supported by it will benefit from the training. Therefore, generalization of training transfer to tasks not trained is expected to be more likely in core process-based training, such as working memory training (WMT), than in strategy-based approaches.

Working memory training

Working memory refers to the cognitive system that can temporally store and manipulate limited amount of information in order to perform ongoing processing of information (Cowan, 2017). Several WM models has been proposed in the literature (for an overview of different models, see Miyake & Shah, 1999) and attempts to identifying benchmarks for the field has been made (Oberauer et al., 2018).

One of the most influential model is the multicomponent model of WM (Baddeley & Hitch (1974), in which the visuospatial and verbal contents are processed in the visuospatial sketchpad and phonological loop, respectively (Baddeley, 2000; Baddeley and Hitch, 1974). The episodic buffer is accountable for binding visuospatial and verbal information as well as long-term memories and the central executive is the component responsible for the allocation of attentional resources to relevant information (Baddeley, 2000; Baddeley and Hitch, 1974).

Working memory is one of the most impaired cognitive functions in elderly people, and it is postulated as one of the sources of the cognitive decline observed in this developmental phase (Park, 2000), mainly because working memory has been seen as a core process for many high-order cognitive functions as reasoning (Shakeel & Goghari, 2017), reading (Just & Carpenter, 1992), prospective memory (Bisiacchi, Tarantino, & Ciccola, 2008), processing speed (Diamond et al., 1999), attention (West, 1999), perceptual organization (Ko et al., 2014), and general language (Kemper, Herman, & Liu, 2004). Hencefore, working memory training (WMT) has been proposed as a prominent intervention with benefits not only in working memory performance, but also in other cognitive domains that share neural or cognitive mechanisms with the trained task (Dahlin, 2009). In accordance, many WMT studies in elderly people have shown evidence of cognitive enhancement and brain plasticity related to the training (for a review, Neely & Nyberg, 2015). However, evidence of far transfer, generalization of the training to

tasks not similar to the trained one, is scarcer (for reviews see Karbach & Verhaeghen, 2014; Melby-Lervåg et al., 2016; Melby-Lervåg & Hulme, 2016).

In the field of WMT, intervention targeting updating of information has drawn researchers' attention. Updating is the ability to hold information, while continually updating the content to be remembered, in a way that information which is no longer needed is dropped and replaced by a new relevant one. Schmiedek, Hildebrandt, Lövdén, Wilhelm, and Lindenberger (2009) have shown a strong latent correlation of .96 between updating (i.e., n-back, memory updating, and alpha span) and complex span tasks (i.e., reading, counting, and rotation span). Both, updating and complex span tasks, are equally predictive of Gf ability.

Updating seems to require both passive store and active processing of WM (Morris & Jones, 1990). The mechanisms are strictly related to Gf as performance of both depends on capacity limits (number of items to be processed in case of WM and number of interrelationships in case of Gf) (Halford, Cowan, and Andrews, 2007). Moreover, both functions share the same neural substrates, i.e., frontoparietal network (Salmon et al., 1996; Kane & Engle, 2002; Takeuchi et al., 2018, Wager & Smith, 2003; Watson & Chatterjee, 2011). Updating ability is reduced in old age and it mediates age-related differences in Gf (Chen & Li, 2007). Therefore, training updating is wagered to have an impact on Gf (Friedman et al., 2006). Additionally, older people seem to benefit most of updating training in comparison to young adults (Pergher et al., 2018).

A common training task in updating WMT is the dual *n*-back. It consists of a task tapping verbal and visuospatial modalities of WM simultaneously, in which the person is presented with a changing stream of information (e.g., position of squares in an array and letters) and must decide whether the current stimulus (for both visual and verbal modalities) matches the stimulus displayed *n* positions back. A study by Jaeggi, Buschkuehl, Jonides, and Perrig (2008) was the pioneer by showing evidence of the potential of the dual *n*-back to yield far transfer on Gf in younger adults. Many other studies were performed in this population since then (for a review, see, Au et. al., 2015). However, only one study was performed with older adults (Salminen et al., 2016). In this study, the authors compared the performance of older and younger adults throughout 14 sessions of dual *n*-back training. As a result, they found that both groups improved throughout training sessions, with young adults having a more pronounced training effect. Moreover, although older adults had a worse performance at baseline compared to young adults, at posttest the older participants performed at the same level as young

adults' baseline, showing the potential of this intervention to reduce age-related cognitive differences. A near transfer effect to another updating task (visuospatial working memory task) was also observed.

Most of the studies assessing the effects of WMT include simple and complex span (eg. Borella et al 2017; Cantarella et al., 2017) or updating tasks (e.g., Bürki et al., 2014) to assess near transfer, while Gf tasks are the most used endpoints to assess far transfer, with the Raven's Advanced Progressive Matrices test being constantly employed in this context (e.g., Cantarella, Borella, Carretti, Kliegel, & De Beni, 2016; Heinzel et al., 2013, 2016; von Bastian & Oberauer, 2013; Xin, Lai, Li, & Maes, 2014; Zinke, Zeintl, Eschen, Herzog, & Kliegel, 2011). Gf is an important outcome because it is a predictor of functioning in many aspects of life, such as social status, expected income, job performance, social outcomes, mortality risk, and life expectancy (Aichele, Rabbitt, & Ghisletta, 2015; Gottfredson & Deary, 2004; Neisser et al., 1996). Additionally, this construct is associated with brain reserve (Schmand, Smit, Geerlings, & Lindeboom, 1997).

The synergetic effect of tDCS coupled with cognitive training

tDCS has been proposed as a nonpharmacological technique to boost WMT (e.g., Martin et al., 2013; Ruf, Fallgatter, & Plewnia, 2017). tDCS is a non-invasive brain stimulation technique, in which a weak direct current (typically 1-2mA) is applied through the cerebral cortex via electrodes placed upon the scalp. tDCS does not induce action potential, however, it modulates the resting membrane potential, introducing variations in the response threshold of the neuron, consequently, modifying neuronal synaptic efficiency (Fritsch et al., 2010). The current flows from the anode to the cathode, with neuronal depolarisation being associated with an increase of the neuronal activity in the area under the anode electrode and a neural hyperpolarization associated with a decrease in the neuronal activity in the area under the cathode electrode (Nitsche et al., 2008, 2003; Nitsche & Paulus, 2001). These alterations depend on the specificity of the stimulation protocol, regarding, namely, duration of stimulation; current density, and direction of the current flow (Carvalho et al., 2015; Monte-Silva, Kuo, Liebetanz, Paulus, & Nitsche, 2010) or yet, the previous level of activity of the recruited neural population. tDCS effects may last after stimulation (Nitsche & Paulus, 2001) and it is associated with mechanisms of long-term potentiation (Nitsche et al., 2003). tDCS is a safe intervention with high tolerability, affordable cost, and few side effects (Gandiga, Hummel, & Cohen, 2006; Solé-Padullés et al., 2006). The most common

side effects associated with tDCS are itching, tingling, headache, burning sensation, and discomfort (Brunoni et al., 2011).

The number of studies assessing tDCS effects in the elderly population have shown a growth over the last years (see Figure 2). The studies reported the tDCS enhancement effects in different cognitive functions, such as, episodic memory (e.g., Sandrini et al., 2019), attentional control (e.g., Hanley & Tales, 2019), and language production (e.g., Madden, Sale, and Robinson, 2019). Fujiyama and colleagues (2014) have yet suggested that the tDCS effects are delayed in older adults. More specifically, they have examined the corticospinal excitability after anodal tDCS applied over the primary motor cortex and have observed a delayed response in which older adults exhibited the largest increase only 30 minutes after stimulation, while young adults presented an immediate post-stimulation peak. The authors suggested that the delay in tDCS effects in the elderly could be a consequence of the deterioration in the microstructures of the aging brain.

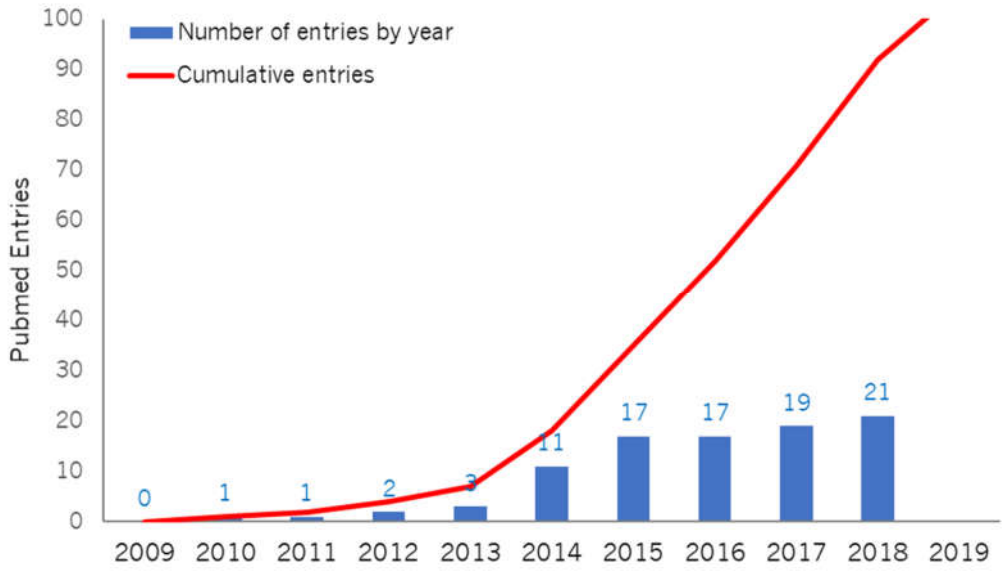

Figure 2. Number of transcranial direct current stimulation (tDCS) articles published per year (2009-2018). *Note.* Data were obtained by searching in PubMed database using the terms ["tDCS" and "older adults"] in title/abstract. Search performed on June 21th, 2019.

Regarding the use of tDCS as an add-on to working memory performance. Fregni et al. (2005) reported that even one single session of tDCS can improve the performance of WM in young adults.

Nevertheless, it is claimed that tDCS effects may be cumulative when applied in repeated daily sessions (Alonzo, Brassil, Taylor, Martin, & Loo, 2012). To the best of our knowledge, only two studies have combined repeated sessions of tDCS with WMT in healthy elderly (Park, Seo, Kim, and Ko, 2014; Jones, Stephens, Alam, Bikson, and Berryhill, 2015). Park et al. (2014) have shown that 10 sessions of anodal bilateral prefrontal cortex improved the accuracy and decreased the reaction time in a working memory computerized program and yielded a near transfer effect assessed by the forward digit span measure. Similarly, Jones et al. (2015) compared the effects of 10 days-tDCS over frontal, parietal or both regions with sham stimulation in WMT. No difference was found in WMT gains in trained and transfer tasks immediately after training. However, only the effects verified in the anodal stimulation groups were sustained a month after training. Nevertheless, due to the limited number of studies addressing the synergetic effect of tDCS with WMT in the elderly, more evidence is necessary to validate this approach in this population.

Additionally, most of studies combining repeated sessions of tDCS with WMT in healthy elderly, have used cognitive tasks as endpoints (e.g., Jones, Stephens, Alam, Bikson, & Berryhill, 2015; Park, Seo, Kim, & Ko, 2014). Thus, studies using other markers are necessary to allow a more holistic understanding of the neural mechanisms underpinning the effects of WMT coupled with repeated sessions of tDCS in aging. Indirect candidates for these markers are the electrophysiological indexes obtained via electroencephalography (EEG) which, in turn, is a tool that could be easily handled in clinical and experimental settings.

Neurophysiological signatures of aging

The identification of a reliable index that precisely detects and quantifies alterations in the cognitive processes related to aging remains challenging (Walker, 2011). EEG patterns could be used to indirectly access those alterations, since it allows the study of brain electrical activity during different cognitive processes (Luck, 2005).

EEG is a non-invasive and safe technique that allows a continuous measure of neural processing with a temporal resolution of a few milliseconds. EEG has been adopted to measure the brain activity of older people, as well as to assess the cognitive training effects in several studies with this population. These EEG analyses ranged from ERPs (e.g., Daffner et al., 2006; Du, Ji, Chen, Tang, & Han, 2018; Küper, Gajewski, Frieg, & Falkenstein, 2017) to oscillatory brain activity (e.g., Jaušovec, & Jaušovec,

2012; Pinal, Zurrón, Díaz, & Sauseng, 2015). In this dissertation, we will use the ERP approach, which consists of a time series of scalp-recorded voltage changes time-locked to a given event (i.e., the presentation of a stimulus) (Kappenman & Luck, 2012; Luck, 2014). More specifically, it is the sum of postsynaptic potentials occurring at the same time in similarly oriented cortical pyramidal cells in response to an internal or external event (Luck, 2005).

The waveforms are a continuous series of positive and negatives peaks, varying in polarity, amplitude, and duration. The division of the waveform in discrete sources of voltages reflecting neurocognitive processes originates the ERP components (Kappenman & Luck, 2012). Each ERP component is associated with particular cognitive processes (for a review, see Luck, 2014). The commonly analysed parameters are latency and amplitude. Most of the time latency is measured as peak latency, which refers to the time spent between the event onset and the maximum amplitude point within a time window, being related to the timing necessary for the execution of a given cognitive process. Amplitude refers to the difference in voltage between the mean voltage of the baseline period and the largest peak of the ERP waveform within a time window (Polich, 2007). Amplitude is related to cognitive processing demands and efficiency.

The most commonly used task to elicit ERPs is the standard oddball task. For the purpose of illustration, in a visual oddball task, a set of two different figures is shown to the participant, one is the target and is less frequently presented (deviant stimulus), while the other figure (standard stimulus) is considered the non-target. Participants have to respond (e.g., mentally counting or pressing a button) whenever they are presented with the target stimulus (for an example of study using a visual oddball task, see Crego et al., 2012). During the analysis, the average of the trials, for standard and deviant stimuli, is extracted for each participant and component, and a grand average may also be extracted across participants.

ERPs is normally classified into two groups: the early components (named sensory or exogenous) peaking around the first 100 milliseconds after stimulus and the later components (termed cognitive or endogenous) which reflects stimulus evaluation related to the processing of information (Sur & Sinha, 2009).

Age-related changes in late endogenous ERP components are well reported in the literature. For example, aging is related to an attenuated and delayed P3b (Dinteren, Arns, Jongsma, & Kessels, 2014; Falkenstein, Gajewski, & Getzmann, 2014; Lubitz, Niedeggen, & Feser, 2017; Pinal, Zurrón, & Díaz,

2015; Schapkin, Gajewski, & Freude, 2014) and abnormalities in this component were observed in mild cognitive impairment and pathological aging (Gu et al., 2018; Lai, Lin, Liou, & Liu, 2010; Olichney et al., 2002, 2008; Waninger et al., 2018; Zurrón et al., 2018). Late positive complex (LPC) differences were also described when comparing older with younger adults (Getzmann, Hanenberg, Lewald, Falkenstein, & Wascher, 2015; ko et al., 2014; Wolk et al., 2009), and healthy older adults and those with cognitive impairment (Waninger et al., 2018) or dementia (Lubitz et al., 2017). Finally, age-related differences in P2 were reported (Bourisly & Shuaib, 2018; Lubitz et al., 2017; Riis et al., 2009; Schapkin et al., 2014; Wolk et al., 2009), as well as differences between normative and unhealthy aging (Waninger et al., 2018).

In light of these results, as well as by a thorough visual inspection of grand average difference waveforms, the components identified for the analyses reported on the current dissertation were the waveforms of positive polarity named P2, P3b, and LPC. Their main characteristics are displayed in Table 1.

Table 1

ERP Components of Interest for the Current Thesis

Component	Peak latency (ms)	Location of maximum effect	Cognitive process	Age-related alteration in amplitude and latency
P2	100-250 ms	Anterior and central	Stimulus evaluation and context updating	Larger latency Mixed results for amplitude
P3b	350-600 ms	Centro-parietal, with maximum amplitude over the midline	Context updating, attentional resources, detection and rating of a stimulus	Lower amplitude and higher latency
LPC	500-800 ms	Centro-posterior	Recognition memory, categorical response, memory match, decision accuracy, and maintenance of a visual working memory representation	Reduced LPC Topography involving additional anterior regions

Note. LPC = Late Positive Complex

Moderators of WMT

Finally, one point that should be considered in WMT practice is the variables that may interfere with the effects. The literature in WMT has pointed out some factors as following: age (Borella, Carbone,

Pastore, De Beni, & Carretti, 2017; Borella et al., 2014; Zinke et al., 2014); education (Borella et al., 2017); general cognitive ability (Borella et al., 2017); baseline performance (Zinke, Zeintl, Eschen, Herzog, & Kliegel, 2011; Zinke et al., 2014); and training duration (Bürki, Ludwig, Chicherio, & de Ribaupierre, 2014; Lilienthal, Tamez, Shelton, Myerson, & Hale, 2013; Stepankova et al., 2014).

Regarding tDCS studies, most of them do not consider interindividual factors (e.g., baseline neuronal state, anatomy, age, brain lesions) in the analysis (for a review see Li, Uehara, & Hanakawa, 2015). However, some studies reported the moderator effects of age (Fujiyama et al., 2014; Heise et al., 2014), education (Berryhill & Jones, 2012), and baseline performance (Katz et al., 2017) in the neuromodulation effects. Therefore, it is important to understand not only if the intervention is effective but also for whom and in which conditions it works best.

Research aims

Taking into account the points outlined in the previous sections, the studies presented in this dissertation aimed to primarily assess the transfer effects of WMT, as well as the add-on effects of tDCS in this intervention, considering the variables that may moderate the effects. Given the need to use different endpoints to measures WMT-induced neuroplasticity, an additional aim of this research was to assess if the ERPs can be used as indexes of Gf, a commonly assessed constructed to infer generalization of WMT. In order to reach the above-mentioned goals, we performed four studies reported in this dissertation as follow:

The first study (Chapter II) aimed to systematically review the literature on the transfer effects of WMT in healthy older adults and to perform a meta-analysis using a robust multilevel meta-analysis technique. This method allowed us to deal with the presence of multiple outcomes in a more sophisticated way, overcoming the limitation of previous reviews in the area. Results are presented and discussed, as well as the factors that moderated the WMT effects.

In the second study (Chapter III), we reviewed studies using tDCS associated with working memory performance in healthy older adults. Only four studies met our inclusion criteria (Berryhill & Jones, 2012; Jones et al., 2015; Park et al., 2014; Seo et al., 2011, demonstrating the incipient interest in this area and the importance of further studies in this field. In this chapter, we presented the included studies, discussing the major findings, and providing recommendations for future studies.

The third study (chapter IV) reports a double blind (with assessor and participant blinded), randomized, placebo-controlled experiment to assess the short-term (i.e., next-day after the intervention) and long-term (i.e., 15 days follow-up) transfer effects of 5-day WMT coupled with tDCS in healthy older adults. Participants were randomly assigned to one of the three groups: 1) WMT (adaptive dual *n*-back task)+active tDCS (2 mA; 20min); 2) WMT+sham tDCS; 3) sham task (visual target detection task)+sham tDCS. Moderator analyses were also included to verify factors influencing the transfer effects.

In the fourth study[†] (Chapter V), we described the electrophysiological correlates of Gf performance in older people. The motivation to perform this study was that, in the future, we will verify the effects of WMT associated with tDCS having an EEG measure to complement the behavioral analysis. As we have used a Gf task to assess generalization of WMT, we want to ensure the association between the ERPs with this construct. This association is well described in young population (Amin, Malik, Kamel, Chooi, & Hussain, 2015; Bazana & Stelmack, 2002; Beauchamp & Stelmack, 2006; De Pascalis, Varriale, & Matteoli, 2008; Duan, Shi, Sun, Zhang, & Wu, 2009; N. Jaušovec & Jaušovec, 2001; Schlottfeldt, Mansur-Alves, Flores-Mendoza, & Tierra-Criollo, 2018; Wronka, Kaiser, & Coenen, 2013; Zhang et al., 2007; Zhang, Shi, Luo, Zhao, & Yang, 2006), but not yet in the elderly. Therefore, it is important to verify this relationship in this phase so that the ERPs, can be used to better understand the combined or individual effects of tDCS and WMT.

In the final sections (Chapters VI and VII), we present our final considerations and conclusions having a summary of the main findings reported in this dissertation, their implications, and plans for future studies, as well as, a reflection on the challenges we have faced in this journey.

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[†] Participants of study 4 were the same participants of study 3, with three more participants included.

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CHAPTER I

INTRODUCTION

Reviewing working memory training gains in healthy older adults: A meta-analytic review of transfer for cognitive outcomes[3]

Abstract

The objective of this meta-analytic review was to systematically assess the effects of working memory training on healthy older adults. We identified 552 entries, of which 27 experiments met our inclusion criteria. The final database included 1130 participants. Near- and far-transfer effects were analysed with measures of short-term memory, working memory, and reasoning. Small significant and long-lasting transfer gains were observed in working memory tasks. Effects on reasoning was very small and only marginally significant. The effects of working memory training on both near and far transfer in older adults were moderated by the type of training tasks; the adopted outcome measures; the training duration; and the total number of training hours. In this review we provide an updated review of the literature in the field by carrying out a robust multi-level meta-analysis focused exclusively on WMT in healthy older adults. Recommendations for future research are suggested.

Keywords: meta-analysis; working memory training; cognitive plasticity; training transfer; healthy older adults; healthy ageing.

[3] Publications derived from this study:

Peer reviewed publications in print or other media

Teixeira-Santos, A. C., Moreira, C. S., Magalhães, R., Magalhães, C., Pereira, D. R., Leite, J., Carvalho, S., & Sampaio, A. (2019). Reviewing working memory training gains in healthy old people: A meta-analytic review of transfer for cognitive outcomes. *Neuroscience & Biobehavioral Reviews. (103):* 163-177. doi: https://doi.org/10.1016/j.neubiorev.2019.05.009

Abstracts, Poster Presentations and Exhibits Presented at Professional Meetings

Teixeira-Santos, A.C., Magalhães, R., Magalhães, C., Pereira, D.R., Carvalho, S., Sampaio, A. (2017). Is working memory training in elderly people effective? A meta-analytic review, Poster session presented at the II International Convention of Psychological Science, Vienna, Austria.

Introduction

Ageing of the world population is a major public health concern that has captured the attention of the general public. Overall, more than 962 million people were over the age of 60 in 2017. It is estimated that this number will more than double to 2.1 billion people by the year 2050 (United Nations, Department of Economic and Social Affairs, 2017). Specifically, it is estimated that the population of people over the age of 80 will triple by the year 2050, increasing from 137 million to 425 million (United Nations, Department of Economic and Social Affairs, 2017). Therefore, much effort has been made to promote optimal ageing to avoid both declines in cognitive functioning and dependence on others, which are factors associated with ageing. Specifically, much has been done to try to reverse age-related cognitive decline and prevent or delay pathological cognitive disorders. This movement represents a significant attempt to improve the quality of life of older adults and to relieve the burden on medical care systems that has resulted from a substantial increase in the elderly population. Efforts to address the issue include non-pharmacological interventions, such as the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial (Ball et al., 2002, Ball et al., 2002; Rebok et al., 2014). The promising findings in the field encouraged researchers to further investigate the benefits of cognitive training in older people.

Different cognitive training approaches are reported in the literature (Jolles & Crone, 2012). They can be classified into two major categories: "strategy-based training" and "process-based approaches". *Strategy-based training* consists of the development of specific adaptations and strategies, such as mnemonics, which can be used to ameliorate daily struggles (Lustig, Shah, Seidler, & Reuter-Lorenz, 2009), whereas process-based approaches focus on the training of specific cognitive abilities (Clare & Woods, 2004). More specifically, *core process-based training* focuses on training central mechanisms with the purpose of producing more substantial effects in functions that depend upon this central processor and that share a common neural substrate (Morrison & Chein, 2011). Notably, working memory training (WMT) has emerged as a proxy for improving cognitive functions (Neely & Nyberg, 2015).

Working memory (WM) refers to the components responsible for maintain temporally a limited amount of information in an available state to allow the processing of ongoing information (Cowan, 2017). WM performance declines markedly with ageing, and this has been associated with abnormalities

on the frontoparietal networks involved in WM, as well as neuromodulatory (dopamine) and neuroanatomical alterations (Bäckman et al., 2017; Bäckman, Lindenberger, Li, & Nyberg, 2010; Lubitz, Niedeggen, & Feser, 2017; Park & Reuter-Lorenz, 2009; Raz, 2005; Rottschy et al., 2012; Salthouse, 1990). This reduction in WM capacity in older adults, along with a decrease in processing speed, seem to underlie age-related cognitive decline (Braver & West, 2008), primarily because WM is associated with higher-order cognitive functions (Unsworth, Heitz, & Engle, 2005), including reasoning (Shakeel & Goghari, 2017), reading (Just & Carpenter, 1992), prospective memory (Bisiacchi, Tarantino, & Ciccola, 2008), processing speed (Diamond et al., 1999), attention (West, 1999), perceptual organization (Ko et al., 2014), and general language (Kemper, Herman, & Liu, 2004). Therefore, given the decrease in WM performance with ageing and its putative role in higher-order cognitive functions, WMT has been studied extensively to enhance cognition in older adults, and positive effects of WMT on both cognition and neural plasticity have been found (Constantinidis & Klingberg, 2016; Karbach & Verhaeghen, 2014).

Experimental studies of WMT typically include an experimental group, whose members participate in a WMT, and a control group. The control group can be a no-contact control group (passive control group) or an active control group that completes a non-related activity or a low-level WMT. Participants in active control group are exposed to a training setting (i.e., number of sessions, contact with the experimenter, a style of intervention) that is similar to that of the experimental group, but they are not exposed to the experimental WM condition. This design with active control condition allows the researcher to control for effects that may result from social contact during the experiment or a participant´s expectations. However, participants from both groups (passive and active control groups) undergo the same testing before and after the intervention as the participants of the experimental groups.

There is abundant literature on WMT (see App. table 4). They may include computerized tasks and can be visual, auditory or both visual and auditory. Trained tasks usually consist of complex or simple span tasks or updating tasks. In complex span tasks, participants must recall a sequence of stimuli, which is interleaved with a concurrent activity. In simple span tasks, participants must remember the sequence of stimuli in forward (fwd) or backward (bwd) order. Updating includes tasks in which participants hold specific content in memory, continually updating the information to be remembered and dropping information that is no longer needed. Training is usually adaptive, i.e., the task difficulty adjusts based on the individual's performance (von Bastian & Eschen, 2016).

Several studies have been designed to study the effects of WMT by comparing the pre- and posttest results of experimental and control groups immediately after training (posttest) and at a delayed post-training assessment (follow-up). Additionally, studies have investigated the transfer effects, i.e., whether training gains can be generalized to other tasks involving different cognitive abilities (e.g., Borella et al., 2010) such as fluid intelligence (Beatty & Vartanian, 2015). Although there are no clear criteria to define transfer distance, most authors locate the generalization of the effects along a continuum of near to far transfer (Noack, Lövdén, Schmiedek, & Lindenberger, 2009). Near transfer consists of an improvement on tasks that are like the trained task and that share the same mechanisms or components, while far transfer represents an improvement on tasks that measure abilities that are not like the abilities trained. Near-transfer effects are commonly observed (Borella et al., 2010; Li et al., 2008), although this is not always the case (Dahlin, Nyberg, Bäckman, & Neely, 2008). Results regarding far transfer are controversial with limited or no evidence (Borella, Carretti, Zanoni, Zavagnin, & De Beni, 2013).

Previous narrative and systematic reviews have debated the potentialities and controversies of WMT (Constantinidis & Klingberg, 2016; Karbach & Verhaeghen, 2014; Lampit, Hallock, & Valenzuela, 2014; Melby-Lervåg & Hulme, 2013, 2016; Morrison & Chein, 2011; Schwaighofer, Fischer, & Bühner, 2015; von Bastian & Oberauer, 2013; Weicker, Villringer, & Thöne-Otto, 2016), yet the results are inconclusive (see App. Table 1App. Table). Therefore, the current meta-analysis aims to contribute to this debate by examining the generalization of training effects to non-trained tasks (near and far transfer) (aim 1) and the maintenance of the effects over time (i.e., at follow-up) (aim 2) by using a meta-analysis approach that is different from the ones used in previous reviews.

Additionally, previous meta-analyses (Karbach & Verhaeghen, 2014; Melby-Lervåg, Redick, & Hulme, 2016) and experimental studies (e.g., Bürki, Ludwig, Chicherio, & de Ribaupierre, 2014; Stepankova et al., 2014; Zinke et al., 2014) have suggested that variables such as type of control group (Melby-Lervåg et al., 2016), age (Borella et al., 2014; Borella, Carbone, Pastore, De Beni, & Carretti, 2017; Zinke et al., 2014), education (Borella, Carbone, et al., 2017), general cognitive ability (Borella, Carbone et al., 2017), baseline performance (Zinke et al., 2014; Zinke, Zeintl, Eschen, Herzog, & Kliegel, 2011) and training dosage (Bürki et al., 2014; Lilienthal, Tamez, Shelton, Myerson, & Hale, 2013; Stepankova et al., 2014) might moderate training gains and transfer effects. For instance, in relation to the type of control group, a meta-analisys from Melby-Lervåg et al. (2016) reported that the type of

control group predicted transfer effects. In particular, studies showed more significant effects when using a passive control group than when using an active control group. However, other meta-analitical studies (Karbach & Verhaeghen, 2014; Weicker et al., 2016) did not find influence of type of control group (active or passive) in transfer effects. Regarding the age, an experimental study performed by Borella et al. (2014) found transfer effects of a visuospatial WMT for measures of STM (short-term memory), WM, inhibition, processing speed, and reasoning only in young-old adults but not in old-old adults. In accordance, together with an age-related difference in the transfer effects, Borella et al. (2017) also documented the role of age as an important moderator of the effects in WMT, although the results varied according to the type of transfer task. In addition, Zinke et al. (2014) evidenced that old-old participants had less gains than young-old participants, except for fluid intelligence in which the reverse pattern was verified.

Borella, Carbone, et al. (2017) have also shown that vocabulary and baseline performance influenced WMT. In this study participants with higher vocabulary scores and poor pretest performance benefited more from training, although this pattern was not the same in all outcomes (e.g., in fwd digit span, lower vocabulary score was related to more benefit in training). Moreover, participants with low levels of baseline performance in WM tasks were likely to benefit more from WMT (Zinke et al., 2014, 2011). Related to session length/duration, Jaeggi et al. (2008) documented a significant growth in far transfer throughout the sessions (from 8 to 19 sessions). Other researchers showed that a group which trained for 20-day outperformed a 10-day training group in a visuospatial measure (Stepankova et al., 2014), while a small positive significant moderator effect for small training dose in comparison to large training dose was observed in a meta-analysis (Melby-Lervåg et al., 2016).

Taken together, in the current study, we verified if the variables as type of control (active/passive), mean age of participants, total number of training hours, number of training sessions, training length in weeks, training type (single training - complex span, simple span, updating, or mixed training: more than one type of WM task), years of formal education, general cognitive ability (operationalized by vocabulary score), and baseline performance would moderate the training effect (aim 3). In addition, we also verified if the type of the outcome adopted (e.g., Cattell; Raven's Advanced Progressive Matrices - RAPM; complex span) would moderate the transfer effect.

Previous meta-analytical work merged the results of different age groups (Mansur-Alves & Silva, 2017; Melby-Lervåg et al., 2016; Melby-Lervåg & Hulme, 2013) or did not include older adults (Au et

al., 2015). This review focuses on only older adults, as WM is markedly affected by ageing (Salthouse, 2000), and WMT is proposed as an innovative approach to counteract age-related cognitive declines (Constantinidis & Klingberg, 2016; Karbach & Verhaeghen, 2014). While merging different ages and conditions may yield sample heterogeneity, this practice can pose some problems for the internal and external validity of the findings (Rothwell, 2006). Additionally, to better isolate the effects of WMT, this meta-analysis addresses the specificity of the training delivered to the experimental groups by including studies whose experimental groups participated in trainings focused exclusively on WM and excluding studies whose experimental groups participated in trainings targeting cognitive functions other than WM. We also excluded papers whose active control groups participated in a non-adaptive WMT that remained always in a lower level of WMT (Brehmer et al., 2011; Chan, Wu, Liang, & Yan, 2015; Loosli et al., 2016; Shing, Schmiedek, Lövdén, & Lindenberger, 2012; Simon et al., 2018; Wayne, Hamilton, Huyck, & Johnsrude, 2016), specific examples include: comparing an adaptive WMT with a WMT whose load (e.g., N = 2 or N = 3) is held constant throughout the training (Brehmer et al., 2011; Chan et al., 2015; Wayne et al., 2016); training both experimental and control groups with a recent-probe and an *n*-back task, with the experimental group receiving trials with higher proactive interference when compared to the control group (Loosli et al., 2016); the participants performed a numerical memory updating task, however different groups were exposed to distinct rates of stimuli presentation (750 ms, 1500 ms or 3000 ms) (Shing et al., 2012). Considering that our aim was to contrast WMT with a placebo training not related to WM (e.g., questionnaire, quiz, visual search) or a non-training condition, in the present review, the above-mentioned studies were not included in the analysis. The rationale behind this is the fact that even a low-level of WM performance activates similar brain areas as high-level of WM processing (Braver et al., 1997; Kawagoe et al., 2015; Ragland et al., 2002). Since we do not have enough information to determine a suboptimal dosage of WMT that would work solely as placebo (Huitfeldt, Danielson, Ebbutt, & Schmidt, 2001), comparing different loads of WMT could lead to less interpretable data as these WM tasks might produce similar effects. As a consequence, we would not be able to isolate gains that are due to WMT (ICH Harmonised Tripartite Guideline, 2000). In fact, as suggested by Brehmer and colleagues (2011), both adaptive WMT and training at low WM load might lead to neural changes. Additionally, although many researchers classify executive function tasks as WM we did not include training of executive functions, such as Stroop interference, verbal fluency or task switching. As claimed by Oberauer et al. (2018) in the Benchmarks for Models of Short Term and Working Memory,

executive functions are framed under specific theories and models that are different from the WM literature. Furthermore, similar to previous meta-analysis (Karbach & Verhaeghen, 2014), we focused on healthy older adults, which represents the majority of the aging population, grounded on the basis of maintenance or enhancement of cognition as a preventive measure, instead of rehabilitation in non-normative aging as a remedial measure (Tkatch et al., 2016).

Regarding the methods carried out in this meta-analysis, we employed robust analytical methods to address multiple outcomes (Moeyaert et al., 2017) rather than use the average of the outcomes (e.g., Karbach & Verhaeghen, 2014; Melby-Lervåg & Hulme, 2016). Robust approaches to address multiple outcomes and treatments are critical as they give unbiased parameter estimates, while the average method may bias the estimates of the standard errors (Moeyaert et al., 2017; Morris, 2008). Finally, a sensitivity analysis was performed to address the lack of data on correlations between pre- and post-training measures. These correlational data are necessary to calculate the variance of the effect size of intervention gains, which was not considered in previous meta-analyses (Mansur-Alves & Silva, 2017; Melby-Lervåg & Hulme, 2016, 2013; Schwaighofer et al., 2015). Finally, a descriptive analysis of the risk of bias was provided following the Cochrane recommendations (Higgins & Altman, 2008). Overall, considering these methodological issues and the fact that new papers have been published since the publication of the most recent meta-analysis, the current study offers an integrated and updated overview of WMT gains in healthy older adults in accordance with the Cochrane recommendations (Higgins & Green, 2008) that highlight the need to update reviews every two years.

Methods

We performed a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) (Moher et al., 2009).

Data sources and eligibility criteria

Five databases (Scopus, Pubmed, PsychINFO, Science Direct, and Scielo; the last was accessed through Web of Science) were searched on January 16, 2019. There were no time or language restrictions. The search terms used were “training”, “working memory”, and “older adult”. The combinations of descriptors can be found in the supplementary material (see table A). Additionally, reference lists from six major reviews and one book chapter in the field were also searched (Karbach &

Verhaeghen, 2014; Melby-Lervåg et al., 2016; Melby-Lervåg & Hulme, 2016, 2013; Morrison & Chein, 2011; Noack et al., 2009; Shipstead, Redick, & Engle, 2012).

App. Table 2 includes the inclusion/exclusion criteria and App. Figure 1 provides a schematic representation of the steps adopted in the literature search. When there were insufficient data to proceed with effect size estimations, an email was sent to the authors requesting the relevant information. In cases in which a reply from the authors was not possible, we limited the inclusion of the study to the data provided.

Data extraction

Two authors selected articles based on the titles and abstracts, and duplicate records were manually removed. After the exclusion of irrelevant articles, two authors independently performed a full-text analysis to assess the eligibility of the articles for inclusion in the review. There was moderate Fleiss' Kappa inter-rater reliability agreement between investigators in the full-text screening, including both included and excluded studies ($k = 0.5$) (Landis & Koch, 1977). Two reviewers independently assessed the risk of bias using the Cochrane Collaboration's risk of bias tool (Higgins & Altman, 2008). Studies were classified as "high risk", "low risk" or "unclear" in the following domains: randomization, concealment of allocation, blinding of participants, personnel and outcome assessment, attrition, and reporting bias. At any stage, disagreements between reviewers were solved with discussions or in consultation with a third reviewer. Statistical analyses were conducted using the R packages "metafor" (Viechtbauer, 2010), "forestplot" (Gordon & Lumley, 2016), "clubSandwich", (Pustejovsky, 2017), and "metaLik" (Guolo & Varin, 2012) from R statistical environment (RStudio, version 3.5.2, R Development Core Team, 2018).

Two reviewers independently recorded the following information from each full-text article: scores, standard deviations of pre-and post-treatment assessments, number of participants per group, types of outcomes, predictor variables, and dropout rates. Completion rates (i.e., the percentage of participants who completed training programmes) were calculated for each group. When a trial had two control groups, an active and a passive, we analysed data from the active group, as it is suggested that this approach allows better control of expectancy effects, such as the Hawthorne effect (Wickstrom & Bendix, 2000). One exception was the study of Weicker et al. (2018), from which the passive control group was

selected instead of the active control group, as the latter performed a fixed low-level WM task (see for exclusion criteria).

To assess near transfer effects, we divided outcomes in STM and WM, as the majority of WM definitions recognize both passive storage and active processing as parts of WM (Cowan, 2017). Additionally, correlations within verbal or spatial domains are higher compared to correlations between domains (verbal/visuospatial) (Cowan, 2017; Oberauer et al., 2018). Accordingly, we divided WM outcomes in verbal and visuospatial categories. Reasoning was adopted as a far transfer outcome due to its strong relationship with WM and due to the fact that it is a commonly used measure in the field (Conway, Kane, & Engle, 2003; Oberauer, Süß, Wilhelm, & Wittmann, 2008). Given that neuropsychological test outcomes varied across studies, they were grouped into broader domains to allow comparisons across studies. A description of each cognitive domain and the corresponding measures is available in app. Table 6 and app. Table 7. A minimum of four articles was necessary to compose a category. For verbal WM, the outcomes were grouped into three categories: bwd simple span; complex span; updating. Visuospatial WM had only the bwd simple span category. For STM, only the category "simple span" was created. Reasoning outcomes were grouped according to the tests used to assess reasoning abilities (e.g., Cattell, Raven's Standard Progressive Matrices – RSPM, RAPM, Leistungsprüfsystem Subtest - LPS).

Multilevel-meta-analysis

Effect sizes were calculated to estimate the transfer effect difference between WMT and control condition. The effect sizes of post-intervention and follow-up gains were calculated using Hedges' g (Hedges, 1989). Since the design used in the individual studies of this meta-analysis have a *pre- posttest control* design, we followed the discussion presented by Morris (2008, p. 369) to calculate the effect sizes measures. More precisely, we used the standardized mean difference described in formula 5, which was originally defined by Becker (1988):

$$g = c(n_{E-1})\frac{M_{post,E} - M_{pre,E}}{SD_{pre,E}} - c(n_{C-1})\frac{M_{post,C} - M_{pre,C}}{SD_{pre,C}},$$

where $M_{pre,E}$ and $M_{post,E}$ are the experimental group pretest and posttest means, $SD_{pre,E}$ is the standard deviation of the pretest scores, $c(m)$ is a bias correction factor, n_E is the size of the

experimental group, and $M_{pre,C}$, $M_{post,C}$, $SD_{pre,C}$, and n_C are analogous values for the control group. The bias correction factor is presented in formula 22 as described in Morris (2008, p. 372):

$$c(m) = \sqrt{\frac{2}{m}} \frac{\Gamma[m/2]}{\Gamma[(m-1)/2]},$$

where Γ is the gamma function. The sampling variances were obtained through equation 13 of Becker (1988). All effect sizes and sampling variances were automatically computed using the R package "metafor".

Unfortunately, accurate estimation of the effect size variance in this formula requires the correlation between pre- and posttest scores, which was not available for most of the studies. Therefore, as recommended by Borenstein (2009), a range of plausible correlations (r = .3, .5, .7) was considered, and a sensitivity analysis was conducted to ensure that the conclusions from the meta-analysis were robust. A table for the sensitivity analysis is provided in the supplementary material (see table C).

In some studies, more than one measure for the same category was adopted within the same experiment (e.g., Cantarella, Borella, Carretti, Kliegel, & De Beni, 2017 reported on two reasoning measures: Cattell and RSPM). In those cases, a multilevel model was adopted for handle multiple effect sizes from the same sample. Using a robust method for dealing with multiple outcomes, such as in the multilevel model or the (robust variance estimation (RVE), is important to avoid bias in the estimates of the effects, standard errors and variances (Moeyaert et al., 2017; Morris, 2008).

Considering that effect sizes from the same study are dependent on one another, a multivariate meta-analysis is recommended to model these dependencies (Harbord, 2011). Indeed, classic meta-analytic models assume independence among effect sizes. However, this assumption is not realistic with clustered data, such as multiple outcomes from the same study. Multilevel models allow for model dependencies due to clustering and are therefore recommended to account for non-independence in the observed outcomes. Classic meta-analytic models can be considered 2-level models, with participants at level 1 and effect sizes at level 2, whereas multilevel models, also called 3-level models, include clusters at level 3.

In this work, we used multilevel modelling that was complemented with both a sensitivity analysis and the RVE method. Specifically, this procedure consisted of two main steps. First, a full sampling variance-covariance matrix was imputed through the function "impute_covariance_matrix" from the

"clubSandwich" package by selecting the studies to be the clusters, and the intra-experiments correlation ρ to be 0.5. Second, the corresponding multilevel multivariate random-effects model was assessed through the function "rma.vm" in the "metafor" package. Unstructured correlation matrices were used to allow random effects to be correlated and to have different variances for each outcome. To ensure robustness of the meta-analysis results, complementary analyses were performed through the RVE method and a sensitivity analysis with different correlations (ρ = 0.3, 0.5, 0.7). Robust results have been obtained through the function "coef_test" from the "clubSandwich" package, following the cluster robust estimator for multivariate/multilevel meta-analytic models described in Hedges et al. (2010). Due to consistent findings observed with these complementary methods, further mixed effects multilevel modelling (using moderators) was only performed for r = 0.5 and ρ = 0.5 (r is the pre- posttest correlation and ρ is the intra-experiment correlation).

The significance of the pooled effect size was determined using a Z test. Effect size was also compared to a t-test with the Satterthwaite correction (Pustejovsky, 2017) and to a likelihood ratio test based on Skovgaard's statistic (Guolo & Varin, 2012) to confirm the validity of the findings. The effect size for each construct is presented in table 1. Forest plots with the distribution of effect sizes were then generated for all constructs and categories (see App. Table 2 and App. Table 3). Visual inspection of graphs, Cochrane's Q test, and the I^2 Index were used to assess heterogeneity in random-effects models. The variance components σ^2_1 and σ^2_2 were used to assess between- and within-studies heterogeneity, respectively, in the multilevel analysis. To address the small number of studies included in some of the analyses, two small sample corrections were performed: Satterthwaite p-values from the RVE (Pustejovsky, 2017), and Skovgaard's p-values from second-order likelihood inference (only for 2-level random effects) (Guolo & Varin, 2012).

Influential outcomes

Influential outcomes are considered outliers that exert a strong influence on the results. To ensure the robustness of the results, influential outcomes were removed from each group with at least four outcomes. They were identified by the function "influence" from the "metafor" package and they are summarized in App. table 8. The analysis of influential studies identified 17 influential outcomes, which were eliminated from the original database.

Moderator analysis

A moderator analysis was conducted with predictors selected from previous literature (Borella et al., 2014; Borella, Carbone, et al., 2017; Bürki et al., 2014; Jaeggi et al., 2008; Stepankova et al., 2014; Verhaeghen, Marcoen, & Goossens, 1992; Zinke et al., 2014), considering their influence in visuospatial and verbal WM and STM, as well as, reasoning for both immediately after training and at follow-up. The following variables have been tested as moderators: 1) type of control (active or passive); 2) mean age of the participants; 3) training dose (total number of training in hours); 4) training length (in weeks); 5) total number of sessions; 6) training type (single i.d., complex/simple span, updating training or mixed training, i.e., combination of more than one type of WM task); 7) years of formal education; 8) category of the outcome (e.g., Cattell; RAPM; RSPM); 9) general cognitive ability (measured by the vocabulary test); 10) baseline performance. In this analysis, we used a 3-level random-effects model to assess the overall effect of WMT in post-test and follow-up for each construct, including each moderator separately.

Publication bias

To assess sensitivity to publication bias in this meta-analysis, different complementary methods were utilized, namely, tests for funnel plot asymmetry (Egger, Smith, Schneider, & Minder, 1997), the trim-and-fill method (Duval & Tweedie, 2000a, 2000b), and the Henmi and Copas method (Henmi & Copas, 2010). The sensitivity analysis of the results was investigated with the "leave-one-out method". Given that publication bias is based on the symmetry of the distribution of the effect sizes in a funnel plot, if we compare very different measures, the distribution is not expected to be symmetric, and it may mislead the analysis. In our sample, studies adopted a large variety of tasks to measure the same construct. Thus, publication bias and the "leave-one-out" method were assessed by the categories of measures. Moreover, asymmetry of funnel plot was verified only in categories having at least 10 experiments, following literature recommendations (Sterne et al., 2011; Zhou, Ye, Tang, & Wu, 2017). Finally, as these methods aim to identify significant differences between individual experiments, no more than one outcome per experiment can be included in a single plot. Therefore, for groups having at least two outcomes from the same trial, all possible combinations of subgroups, including exactly one outcome per trial, were considered to assess publication bias and the "leave-one-out" method. Funnel

plots with the effect sizes of the included studies in all comparisons can be found in the supplementary material section (see figure A).

Results

The results are described in four major sections. First, we describe the different studies that were included in the analysis. Second, we present the small-study effect analyses. The third section targets the main aim of this review which was to verify the WMT effectiveness at posttest and follow-up together with the moderator analysis. Finally, the risk and publication bias results are presented.

Characteristics of included studies

We identified 300 studies (after removal of duplicates), from which 217 were excluded after reading the abstract and 59 after the full-text analysis. Criteria for paper exclusion: a) review paper; b) sample of non-human animals; c) young participants or elderly but not cognitively healthy participants; d) training does not exclusively target WM; e) the active control group performed a WM task; f) absence of control group; g) studies whose sample has been previously used in a another study already included in the meta-analysis; h) WMT coupled with transcranial direct current stimulation (tDCS); i) incomplete data. Twenty-four articles (27 experiments) met the inclusion criteria (for a list of the included papers, see table B in the supplementary material) and were selected for the quantitative analysis, which included data for up to 1130 participants. All trials were published in the last ten years, with *Psychology and Aging* as the journal with the highest number of publications.

The mean age of the participants ranged from 62.9 to 87.1 years (M = 69.5, SD = 4.9), and years of formal education ranged from 6 to 17 (M = 12,7 years, SD = 2.85). Of these studies, 79% were carried out in Europe (n = 19), with the remainder conducted in North America (n = 3; 13%) and Asia (n = 2; 8%). On average, studies implemented 12 training sessions (SD = 8.59; range = 3 - 40), corresponding to seven total hours (SD = 4.36; range = 1.5 - 20), with a mean session duration of 42 minutes (SD = 13.8; range = 20-60), and an average of three days of sessions per week (SD = 1.36; range = 2 - 7). Follow-up was reported in eight papers, with a mean of eight months after training (SD = 4.4; range = 3 - 18). The completion rate for the whole sample ranged from 70 to 100%. Most of the training was performed in laboratory settings (n = 16); however, six trials were conducted at participants' homes. This information was not detailed in three papers (Richmond, Morrison, Chein, & Olson, 2011;

Xin, Lai, Li, & Maes, 2014). In eight studies, participation was voluntary, one study included both pay and voluntary participation, ten articles reported financial compensation, and five papers did not mention this information.

Regarding the type of trained task (see App. table 4), studies were grouped into three major categories (Schmiedek, Hildebrandt, Lövdén, Wilhelm, & Lindenberger, 2009; Shipstead et al., 2012): complex or simple span task; updating; mixed (i.e., participants were trained on more than one type of WM task). Eight studies included a complex span task, participants were trained on a simple span task in one study (Zinke et al., 2011), and updating training was observed in ten studies. Five studies had mixed training. Regarding the modality of training (verbal vs. visuospatial), 10 studies included training with verbal stimuli, five included training with visuospatial stimuli, and the remaining nine were crossmodal. All studies, except Pergher, Wittevrongel, Tournoy, Schoenmakers, & Van Hulle (2018), Xin et al. (2014), Zając-Lamparska & Trempała (2016), had adaptive training. Fourteen articles had an active control group, while ten had a passive control group (PCG). As seen in App. table 3, characteristics regarding type of training and control, outcomes and follow-up varied across studies.

Heterogeneity indexes among studies in the different analyses were low to moderate (Higgins, Thompson, Deeks, & Altman, 2003). However, we opted for the random model considering the clinical and methodological heterogeneity found among studies (Higgins & Green, 2008). Before proceeding to the meta-analysis, small-studies effects were explored. The comparison between random-effect modelling, fixed-effect modelling and the Henmi and Copas method were conducted to address this issue. The results of this analysis are summarized in App. Table 9. The conclusions of the three models produced very similar results, and in 71% of the cases the difference was ≤ 0.001, not affecting the significance of the results. The most distinct case happened for verbal complex span at posttest, for which the mean effect from the random-effects model was 0.34, 95% CI = [0.09, 0.58], and the common effect from the fixed-effects model was 0.31, 95% CI = [0.14, 0.49]. In both cases, confidence interval (CI) did not include zero, confirming its statistical significance. Additionally, sensitivity analysis confirmed that the meta-analytic findings were robust regarding the tested correlation coefficients. Indeed, by visual inspection of the table C in the supplementary material, it is possible to observe that when the correlation is assumed to be lower, at $r = 0.3$, or higher, at $r = 0.7$, the estimated summary effect varies by no more than 0.04.

WMT efficacy and moderator analysis

In this section the results from the effect of WMT on transfer task immediately after training (aim 1) and at follow-up (aim 2), as well as, a moderator analysis (aim 3) will be presented. Results from the classical *p*-value or those corrected for small samples (Skovgaard's and RVE) did not differ considerably, so we reported the multi-level *p*-value in the text and all the values in Table 1. The comparisons only had a small difference between the multi-level p-value (p = .03) and the RVE (p = .06) for visuospatial WM in posttest and the multi-level *p*-value (p = .04) and RVE p-value (p = .08) for verbal WM at follow-up. Therefore, the results regarding visuospatial WM in posttest and verbal WM at follow-up should be interpreted with more caution.

We did not find any significant difference between the control types (passive *versus* active control groups) in the moderation analysis (see App. Table 10), except for visuospatial WM at posttest. Additionally, we performed a sensitivity analysis, running the analysis separately for passive and active control groups. The comparison with both passive and active control group merged did not yield an effect size greater than when we performed the comparison of experimental group with studies that included only an active control group, except for visuospatial WM at posttest. Many of the included trials had passive control group (n = 10). If we had excluded those trials from the analyses, some of the comparisons would have a very few studies, decreasing the power of the analyses. Accordingly, the results from both control groups were merged into a single control condition. The effect sizes were calculated comparing the experimental condition with the merged control condition.

Aim 1: examining the generalization of training effects to non-trained tasks (near and far transfer).

WMT effects were examined on near transfer constructs (visuospatial and verbal WM, and visuospatial and verbal STM) as well as on a far transfer construct (reasoning) immediately post-training.

Verbal WM: A significant transfer effect was identified for verbal WM (0.23; 95% CI [0.07, 0.39]).

Visuospatial WM: A significant transfer effect was identified for WM in the visuospatial modality (0.23; 95% CI [0.03, 0.43]).

Verbal and visuospatial STM: No significant transfer effects were identified for verbal (0.16; 95% CI [- 0.05, 0.36]) or visuospatial STM (-0.03; 95% CI [- 0.39, 0.32]).

Reasoning: For reasoning, the effects were not significant (p = .08) at posttest (0.10; 95% CI [- 0.03, 0.23]).

Aim 2: verifying the maintenance of the effects at follow-up.

Concerning the long-term effects of WMT, we observed that the effects were also observed during follow-up to verbal WM (0.23; 95% CI [0.01, 0.46]). However, in visuospatial WM analysis, the effect was not significant (0.14; 95% CI [- 0.09, 0.37]). Regarding reasoning, results were also not significant (0.13; 95% CI [-0.09, 0.35]), as well as for verbal STM (0.18; 95% CI [- 0.10, 0.45]) and visuospatial STM (-0.04; 95% CI [-0.33, 0.25]).

Aim 3: testing moderator variables.

Here we examined if the variable age, training dose, number of sessions, training type, training duration, years of formal education, vocabulary score, baseline performance and type of outcome might moderate training effects. The results are presented in Table . The moderator analysis was significant ($p < .05$) for number of sessions, training length (in weeks) and training dose (in hours), i.e., the gains in reasoning and verbal STM immediately after training are small when training duration increases. Additionally, while the effect of WMT on verbal STM was linearly moderated by training hours and training length, the effect of WMT on Reasoning-posttest was also moderated by the former factors together with the number of sessions. Table 2 outlines these moderator roles. Indeed, the approximation by higher polynomial degrees were also assessed but, in each case, no significance advantage over the linear approach was observed. Specifically, no asymptotic behaviour was detected, as such characteristic would imply a significant variation in the rate of change of the WMT effect with respect to the corresponding independent variable.

Table 1

Effects of Working Memory Training Compared with Control Group by Construct

	Construct	No. of effects (k)	No. of studies (clusters)	Estimate	RE mean				Q-test	I^2 (%)	τ^2	σ^2_1	σ^2_2
					95% CI	*p*-value	Skovgaard's p-value	RVE *p*-value					
POSTTRAINING	Reasoning	33	24	0.10	[-0.026,0.233]	.12	NA	.13	28.53	11.51	NA	0.01	<0.01
	Verbal WM	40	20	0.23	[0.065,0.392]	.006 **	NA	.01*	88.79 ***	56.13	NA	<0.01	0.09
	Visuospatial WM	13	10	0.23	[0.029, 0.426]	.025 *	NA	.06^	16.03	17.83	NA	0.02	<0.01
	Verbal STM	12	11	0.16	[-0.045,0.363]	.13	NA	.16	12.41	14.07	NA	<0.01	0.01
	Visuospatial STM	6	5	-0.03	[-0.388, 0.324]	.86	NA	.74	09.06	45.24	NA	<0.01	0.08
FOLLOW-UP	Reasoning	12	10	0.13	[-0.085, 0.347]	.24	NA	.27	9.36	6.37	NA	0.01	<.01
	Verbal WM	17	9	0.23	[0.006, 0.457]	.04 *	NA	.08^	18.59	16.35	NA	0.01	0.01
	Visuospatial WM	11	8	0.14	[-0.089, 0.368]	.23	NA	.14	6.04	<0.01	NA	<0.01	<0.01
	Verbal STM	6	6	0.18	[-0.097, 0.452]	.205	.983	.19	3.85	<0.01	<0.01	NA	NA
	Visuospatial STM	6	5	-0.04	[-0.334, 0.245]	.763	NA	.72	3.17	NA	NA	<0.01	<0.01

Note. ^p<.1, *p<.05, **p<.01, ***p<.001. NA – Not applicable (only for groups from the same experiment). I^2 – total heterogeneity / total variability; τ^2 – estimated amount of total heterogeneity; σ^2_1 – Variance component of the 3-level model for the between-studies heterogeneity; σ^2_2 – Variance component of the 3-level model for the within-studies (effects within studies) heterogeneity. RVE – Robust variance estimation. Number of studies may be smaller than number of effects because each study may have more outcomes for the same construct. RVE and Skovgaard's (only for 2-level random effects) were applied as a sensitivity analysis to check the robustness of the model. *P*-values did not differ substantially across these analyses indicating the validity of the model.

Regarding the training type, we observed that the studies that included mixed training (i.e., having more than one type of WM tasks) had smaller effects on reasoning immediately after training than the training of updating or complex span tasks alone. Additionally, studies having the Cattell Test as an outcome displayed a higher gain than studies that used other measures in posttest (RAPM; RSPM; LPS). For verbal WM, the gains were higher in complex span tasks than in simple span and updating tasks at posttest. Type of control group was a significant moderator for verbal WM at posttest, with the effect size of studies using a passive control group being higher than studies that used an active control group. Finally, baseline performance moderated the effects on visuospatial STM at immediate posttest, with participants with lower performance showing more benefits with the training.

Table 2

Moderator Effects (Significant Results)

Construct	Moderator effect	Estimate	SE	*p*-value	QE	QM - Test of moderators	σ^2_1	σ^2_2
Reasoning at immediate posttest	Measure - Cattell	0.39	0.14	.005**	20.70	7.82 **	<0.01	<0.01
	Training dose (hours)	-0.04	0.01	.001 **	17.46	11.040 ***	<0.01	<0.01
	Number of training sessions	-0.02	0.01	.004**	20.17	8.35**	<0.01	<0.01
	Training length (in weeks)	-0.11	0.04	.004 **	20.38	8.15 **	<0.01	<0.01
	Training Type - Mixed	-0.41	0.13	.001**	18.36	10.16 **	<0.01	<0.01
Verbal WM at immediate posttest	Measure – Complex span	0.27	0.13	.046 ***	80.67	4.00 *	<0.01	0.08
Visuospatial WM at immediate posttest	Control – PC – AC	0.54	0.24	.023*	10.86	5.17 *	<0.01	<0.01
Verbal STM at immediate posttest	Training dose (in hours)	-0.04	0.02	.043*	8.33	4.08*	<0.01	<0.01
	Training length (in weeks)	-0.11	0.05	.033*	7.89	4.53*	<0.01	<0.01
Visuospatial STM at immediate posttest	Baseline performance	-0.06	0.02	.01*	2.33	6.73**	<0.01	<0.01

Note. $*p < .05$, $**p < .01$, $***p < .001$; σ^2_1 – Variance component of the 3-level model for the between-studies heterogeneity; σ^2_2 – Variance component of the 3-level model for the within-studies heterogeneity. QE – test for residual heterogeneity when moderators are included. QM – test statistic for the omnibus test of coefficients**.** Moderator effects with non-significant results were not presented, they were mean age of the participants, years of formal education, vocabulary performance. Analyses of follow-up did not have any significant moderator.

In summary, WMT had a small significant and long-lasting effect on verbal WM (specifically on complex span outcomes). For visuospatial WM, gains were only observed at posttest, but not at follow-up. Far transfer for reasoning was not observed. Training length, number of sessions, training dose (total training duration in hours), type of training and adopted outcomes (Cattell; and complex span), type of control group and baseline performance appeared as significant moderator variables at posttest assessment.

Publication and risk of bias

Assessment of risk of bias is important when performing a review because it is an index of the quality of included data, and it could also explain heterogeneity when it is highly observed (Viswanathan et al., 2008). Two authors independently assessed the risk of bias. In general, we observed a substantial absence of information for most studies, which limited the ability to classify the risk of bias. Considering the randomization processes (selection bias), 19% of the studies presented risk of bias, whereas in 74% the risk of bias was not clear. Seven percent of the studies adequately reported random sequence generation. Regarding allocation concealment, 22% presented a high risk of bias, 7% adequately reported data, and the remaining 70% did not report on allocation concealment. For blinding (performance bias), 30% of the studies had low risk of bias (compared with 30% with high risk), and 40% of the studies did not mention blindness procedures. Seventy percent of the studies did not exclude data from participants

who dropped out or with missing data. Fifteen percent had high risk of incomplete outcome data, while this was not clear in 15% of the studies. Generally, the studies had high completion rates (ranging from 86% to 100%), although the completion rate was not clear for all studies. Similarly, most articles (93%) reported all outcomes, although they did not state which outcome was the primary. Seven percent presented high risk of selective reporting. Additionally, the lack of adequate correction for multiple comparisons and for baseline group differences were other potential bias observed here. Another possible source of bias was the lack of appropriate screening measures of cognitive decline and of affect disorders such as anxiety and depression. A summary graph of the risk of bias is displayed in App. Table 3 Analysis of publication bias assesses if the set of evidence is biased due to the fact that positive findings are more likely to be published. The analysis of several methods of publication bias (trim-and-fill, leave-one-out, asymmetric tests, and Hemni and Copas) suggested a small presence of publication bias, although it did not seem to substantially alter the results. Trim-and-fill is a method that estimates the number of studies missing in the funnel plot (Duval & Tweedie, 2000b). It was only used in analyses with at least 10 studies; otherwise, the test would not have sufficient power to verify asymmetry (Sterne, Egger, & Moher, 2008; Zhou et al., 2017). This analysis suggested the presence of publication bias in only two cases (simple span and complex span at posttest). Additionally, given that the big issue of publication bias is that the positive results are more representative in the published literature (Mlinarić, Horvat, & Smolčić, 2017), it is important to highlight that trim-and-fill method identified only two cases of missing studies (verbal simple span STM and verbal updating WM, both at posttest), however the effect sizes of the corresponding categories were not significant in verbal simple span STM and verbal updating WM at posttest.

The leave-one-out method was performed by a sensitivity analysis where one study at a time was removed from the analysis to verify the influence of a single study in the finding. This method showed sensitivity of results to individual studies in three cases (verbal fwd simple span at posttest; Cattell and verbal complex span at follow-up). However, in the first two cases, the elimination of a unique experiment would cause a significant pooled effect size, while only for complex span the elimination of a study (among three) would cause a nonsignificant result. Asymmetric tests indicated publication bias in only one case (verbal simple span at posttest), the same comparison already identified with the trim-and-fill method. Finally, in all cases, the Hemni and Copas robust estimation was not significantly different from

the random-effects results, showing that publication bias did not change the overall meta-analytic effects in a significant manner. Therefore, the positive effect of publication bias was not a big issue here.

Overall, the presence of bias did not seem to influence the results as supported by the former publication bias methods (see App. table 9), as well as, by the similarity between effect sizes of studies that presented more criteria classified as high risk of bias (see app. figure 3) (e.g., Goghari & Lawlor-Savage, 2017; Heinzel et al., 2016; Stepankova et al., 2014; Zinke et al., 2011) and those having a lower risk of bias (e.g., Borella et al., 2013; Borella, Carretti et al., 2017b; Guye & von Bastian, 2017; Lange & Süß, 2015; Weicker et al., 2018).

Discussion

This meta-analytical review aimed to verify the gains of WMT on transfer measures in healthy older adults. In contrast to previous meta-analyses, we used different analytical methods to address multiple outcomes and the lack of correlation reports. Additionally, a description of the studies included in the review is provided along with a comprehensive overview of different studies in the WMT field.

The high variability between the experiments challenged data aggregation and, consequently, data interpretation. The studies presented different experimental and control tasks (see App. table 4 and App. Table 5), different outcomes (see App. Table 7), and training protocols. Follow-up also varied broadly across trials, although it was seldom included in the experimental protocol (see App. Table 3.

Regarding the results of the effectiveness of WMT at posttest (aim 1), participants assigned to a WMT group displayed a small significant near transfer effect size of 0.2 for verbal and visuospatial WM, compared to the participants who received a placebo or non-intervention. These results are in line with previous meta-analyses that have shown small to medium near effect sizes immediately after training (Karbach & Verhaeghen, 2014; Melby-Lervåg & Hulme, 2013; Melby-Lervåg et al., 2016). For example, Karbach and Verhaeghen (2014) observed a small near effect size of 0.3 after removal of publication bias (trim-and-fill method). We also observed that WMT had no significant impact on STM, which conflicts with the results of previous research (Schwaighofer et al., 2015). These differences among studies may be due to methodological differences, as Schwaighofer and colleagues (2015) included older adults as well as children and young adults. Moreover, it might be the case that the lack of effect in STM may be due to a preservation of this ability with age (Nittrouer, Lowenstein, Wucinich, & Moberly, 2016; Olson et al., 2004). Therefore, there is less room for transfer in this ability after WMT. Nevertheless, this

hypothesis needs to be further explored as there was one study showing a strong positive effect of WMT on STM (Heinzel et al., 2013). As we observed in the moderator analysis, variables such as the training dose and length, as well as, baseline performance interfered with the effects, which may cause heterogeneity across studies. For the reasoning, there was no significant transfer effect. In fact, a previous meta-analysis (Karbach & Verhaeghen, 2014) only yielded a "marginally significant" far transfer effect that was not fully corroborated by our study with a greater number of WMT trials included in the analysis.

With respect to the WMT long-term effects (aim 2), only ten studies reported follow-up assessments; therefore, the results should be considered with caution. Near transfer effects seem to be maintained at follow-up only for verbal WM. These results are in agreement with Schwaighofer et al. (2015) and partially consistent with Melby-Lervåg et al. (2016, 2013), who only observed a significant maintenance effect in WM outcomes.

We performed a moderator analysis with the following variables as moderators of transfer effects on STM, WM and reasoning at posttest and follow-up (aim 3): 1) type of control (active/passive); 2) the mean age of participants; 3) training dose (total number of training in hours); 4) training length (in weeks); 5) number of training sessions; 6) training type (single: complex span or updating; mixed training: more than one type of WM task); 7) years of formal education; and 8) category of the outcome (e.g., Cattell; RAPM; complex span); 9) vocabulary score; 10) baseline performance. The variables that explained heterogeneity of the effect sizes in reasoning at posttest were the category of the outcome (i.e., Cattell), training length/dose, number of training sessions, and training type (i.e., mixed training). For verbal WM at posttest, the category of the outcome (i.e., complex span) was the variable that explained heterogeneity of the effect sizes. This means that studies having complex span as outcome found more positive effects than studies using another WM measures. For visuospatial WM at posttest, the type of control group (active versus passive) was a significant moderator, with studies using passive control groups presenting higher effect sizes. For verbal STM at posttest, training length and hours were the significant moderators. For visuospatial STM at posttest, baseline performance moderated the results, with participants with lower performance gaining more with the training.

The fact that some measures (i.e., Cattell Test and Complex Span Task) displayed more significant effect sizes than others in the moderator analysis highlights the role of the measures to evaluate the training effects. For reasoning, the effect size on the Cattell Test was significant, showing a positive

moderation effect of this test on far transfer. This result is in line with the results of previous reviews which showed a slightly larger effect of the Cattell Test compared to Raven's Test (Mansur-Alves & Silva, 2017). This finding could be explained by the fact that the Cattell Test consists of different subtests (series, analogies, matrices and classification), which may position it as a more complete indicator of reasoning compared to tests that only have figural type items (e.g., Raven's), as postulated by Gignac (2015). Furthermore, this result is consistent with the claim of Shipstead et al. (2012) regarding the importance of having different instruments to assess transfer effects in the experiments, ensuring that all facets of the construct are assessed.

Considering the moderation effect of training duration/length, either in reasoning or verbal STM, we found unexpected results. For both variables, the results showed a significant negative effect, i.e., that more training duration (total number of hours and length) produced smaller effect sizes. Other variables probably influenced this analysis, such as the type of training performed: most of the shorter duration studies applied the same training task which may be more effective than the training adopted by the long-duration studies (Borella, Carbone, et al., 2017). It is also noteworthy that only one study had higher dosages of training (more than 15 hours) (Goghari & Lawlor-Savage, 2017), whereas six out of twenty had only three sessions (Borella et al., 2014, 2010, 2013; Borella, Carretti, et al., 2017; Cantarella, Borella, Carretti, Kliegel, & De Beni, 2017; Cantarella, Borella, Carretti, Kliegel, Mammarella, et al., 2017). Previously, Karbach and Verhaeghen (2014) and Melby-Lervåg and Hulme (2013) failed to find a significant influence of total training duration in effect size, except for one measure, the Stroop task in Melby-Lervåg and Hulme (2013). In contrast, Schwaighofer et al. (2015) found a positive influence of total training duration on visuospatial STM and of session duration on verbal STM. Weicker et al. (2016) documented a positive correlation between the number of sessions and the effect sizes. In this case, the authors compared two groups (> 20 sessions vs. < 20 sessions) and observed that more training sessions produced larger effect sizes. Nonetheless, the total number of hours was not related to the effect size (> 10 hours vs. < 10 hours). Finally, similar to our results, a previous meta-analysis on video-game training have shown that short training produced stronger effects than long training (Toril, Reales, & Ballesteros, 2014). These discrepant findings need to be further addressed in new randomized controlled trials.

Other factors such as motivation and performance anxiety should also be considered (Delphin-Combe et al., 2016; Jaeggi, Buschkuehl, Shah, & Jonides, 2014). As participants are older adults, some

of them may be unfamiliar with the use of computers (most of the trainings are computerized), and long training durations may lead to demotivation (Laguna & Babcock, 1997). Additionally, participants might not be receptive to extensive training because the training would compete with their other activities for time. Another finding worth considering is the fact that mixed training negatively moderated the effects on reasoning. In other words, the experience of different tasks in the same programme may be less effective than repeating the same task or similar tasks during the training (for similar results, see von Bastian et al., 2013). Perhaps targeting a specific process during training yields sizeable gains, whereas multi-WM processes training may lead to a competition for resources that underpin the transfer effects.

In short, considering the aim 1 (effectiveness at posttest), our results supported only the presence of near transfer effects. For the aim 2 (effectiveness at follow-up), our results supported the maintenance of near transfer effects only on verbal WM. For the aim 3, our data suggested that the type of outcome (Cattell and complex span), training duration/length/number of sessions, baseline performance, type of control group and type of trained task (mixed task) moderate the transfer effects.

Melby-Lervåg and Hulme (2016) identified two main problems with previous meta-analyses that showed promising effects of WMT (Au et al., 2015; Karbach & Verhaeghen, 2014). The first was related to the calculation of a mean effect size without considering the baseline performance. It is noteworthy, however, the absence of correlations between baseline and posttest assessment in the original papers challenges the calculation of the Hedge's *g* change variance. To address this issue, in this review, the effect size calculation was based on the pre- to posttest score difference (Borenstein, Hedges, Higgins, & Rothstein, 2009; Morris, 2008), and we also ran a sensitivity analysis with different values of correlation coefficients.

The second problem pointed out by the authors was the importance of comparing studies with active versus passive control groups. To address this, we performed a moderator analysis with the type of control as moderator which showed a significant effect only for visuospatial WM at posttest (see App. Table 10). We also ran a sensitive analysis with active and passive control group separately (see supplementary material, table D). The effect sizes did not change considerably from the previous results with the merged control group. The exception was the visual WM at posttest in which the results became insignificant. In this analysis, results from RVE and multi-level *p*-value also differed from each other showing that this finding needs further evidence. Moreover, it is noteworthy that one influential study with a big positive effect size (Borella et. al., 2014 – experiment 1) was excluded. If we had kept this

study, the analysis would be significant either case. Probably there is in fact an effect in the visuospatial WM, however given the inconsistency in different analysis, it is not possible to draw a clear conclusion.

In contrast, in the study of Melby-Lervåg and Hulme (2016), some of the meta-analytical results changed when the analysis was performed separately for active and passive control groups. Our findings partially corroborated the results of Weicker et al. (2016), Melby-Lervåg and Hulme (2013), and Karbach and Verhaeghen (2014) that did not find a significant influence of the type of control condition in the outcomes. It is noteworthy, however, that Melby-Lervåg and Hulme (2016) had a diversified sample, including a broader range of ages and learner status within the same analysis, which may explain the differences found.

Relatively to the assessment of risk of bias, most authors did not report data regarding random sequence generation, allocation concealment, and blinding. Among the other risks of bias identified, some trials have performed multiple outcome comparisons without correction or did not use validated screening measures of cognition and affect. Other experiments showed differences between conditions at baseline, most likely due to inappropriate randomization. Some studies were exploratory, not stating primary/secondary analysis nor including a priori sample size calculations. Nonetheless, in the current review, the risk of bias was not problematic since the same pattern of results was found both in studies that fulfilled most of the criteria and in studies that satisfied only a few. Additionally, more recent studies considered this limitation and implemented a more appropriate experimental design (Guye & von Bastian, 2017; Weicker et al., 2018).

The primary limitation of this review is the fact that we pooled different methodological studies together. However, we have done moderator analyses and combined outcomes in categories to address this variability. Second, although we considered a Ph.D. thesis, we did not perform an extensive grey literature search, which may have introduced publication bias in our analysis. It is noteworthy, however, that publication bias analysis did not indicate a strong presence of such bias, especially regarding positive statistical effects. Third, in some comparisons, we had a low number of trials included ($n < 10$), especially with follow-up analyses. Fourth, some of the included studies had a small sample in each comparison ($n < 20$). Even though, this limitation was addressed in the analysis by applying corrections for small samples to the effect size calculation. Fifth, two studies were not included due to the lack of replies from the contacted authors (missing data). Finally, our results may not be valid for the whole ageing population because most studies were conducted with a selective population. To illustrate, most

trials had participants with a high level of schooling (*M* = 12.67 years), and most of the trials had younger older adults as participants (*M* = 69.55). Therefore, additional studies with older populations and participants with lower levels of schooling are needed (e.g., da Silva & Yassuda, 2009; Golino et al., 2016).

Finally, some recommendations are suggested for future studies in the WMT field. New trials should address different training formats that are best suited for the elderly (i.e., optimal session duration, total intervention time and intervals between sessions) (e.g., Penner et al., 2012). Another critical point is related to the importance of increasing the training level of difficulty. In our sample, 95% of the trials were adaptive, meaning that the trained task was adjusted in difficulty according to the participants' performance. However, von Bastian and Eschen (2016) found that participants did not perform better with adaptive tasks than with tasks of self-selected difficulty. Furthermore, a next step could be to compare different WMT programmes as illustrated by Basak and O'Connell (2016), who showed a superiority effect of an unpredictable memory updating training over a predictable one. We also encourage comparisons between web-based interventions and more traditional laboratory approaches (Schwaighofer et al., 2015). Subsequently, researchers should verify how to keep participants engaged in the training programmes. For example, group cognitive trainings could be more motivating then individualized trainings (Kelly et al., 2014). Other approaches such as combining techniques (e.g., non-invasive electrical brain stimulation or physical exercise) could boost WMT effects (Oswald, Gunzelmann, Rupprecht, & Hagen, 2006; Teixeira-Santos, Nafee, Sampaio, Leite, & Carvalho, 2015).

Protocols should be designed to follow participants over more extended periods of time. The outcomes selection could also be rethought. Namely, we could have different outcomes to assess different facets of the same construct (Weicker et al., 2018), and we could account for more clinical relevance and external validity. For example, some promise has been seen regarding the generalizability of results for real life: Cantarella, Borella, Carretti, Kliegel, and De Beni (2017) used everyday problem solving and timed basic daily activities as outcomes; Lange and Süß (2015) had questionnaires for cognitive failures in everyday life; Takeuchi et al. (2014) assessed the effect of WM training on emotional states; and Borella, Cantarella, Carretti, De Lucia, and De Beni (2019) assessed transfer for everyday life in old-old participants. Eventually, subjective cognitive functioning could be included. Similarly, surrogate outcomes, such as magnetic resonance imaging and electrophysiological recordings, could

be used to support the efficacy of the intervention and to define the best training protocol regarding brain plasticity (Buschkuehl, Jaeggi, & Jonides, 2012; Dahlin, Neely, Bäckman, & Larsson, 2008; Heinzel et al., 2016; Takeuchi et al., 2013, 2014).

Other factors that may moderate gains (e.g., motivation; personality; financial compensation) should be further scrutinized (Au et al., 2015; Borella et al., 2013; Zinke et al., 2011). Regarding the population, studies with different age and formal education subgroups are warranted. To the best of our knowledge, no former study in the field has been conducted with illiterate people, mainly because few studies are carried out in developing countries. However, this group is more vulnerable to cognitive decline (Brucki, 2010) and in need of cognitive care opportunities. Finally, regarding risk of bias, future studies should be careful about the proper implementation of the randomization process, allocation concealment, blinding, incomplete outcome and data reporting.

Conclusion

Neuroplasticity, the brain and behavioural capacity of restructuration according to environmental demands, is verified even in late stages of development (Landi & Rossini, 2010), and WMT has been studied as a promising tool to promote it. Our analysis suggested the generalization of WMT to near transfer tasks. Far-transfer effects were not verified, except for the studies whose Cattel Test was used to assess reasoning. Moderator analysis did not show the influence of type of control group (active versus passive), except for one comparison: visuospatial WM at posttest. Importantly, the adopted measures, type of training, training length and duration, baseline performance were significant variables moderating the effects sizes. Overall, the generalization of WMT seems to be limited to the WM construct (see figure 1).

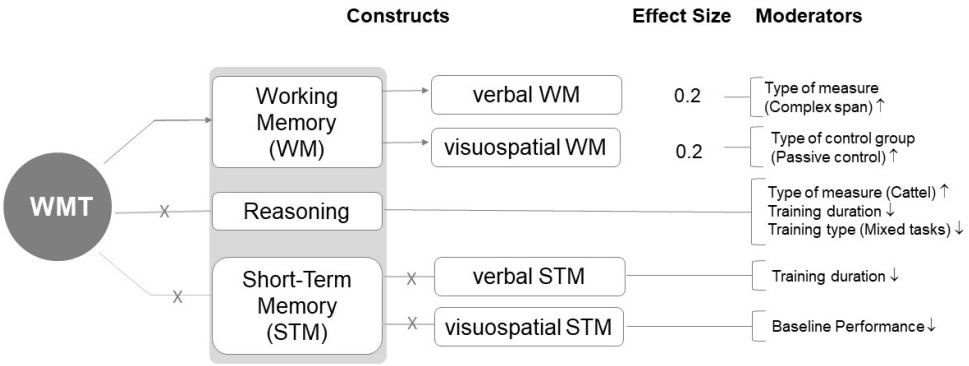


Figure 1. Schematic representation of the main findings of the current meta-analysis. X = non-significant results; Solid line = significant results; ↓ = negative moderating effect;↑ = positive moderating effect.

App. Table 1

Main Findings of Previous Reviews of Working Memory Training Including Older Adults

Study	Near transfer (effect size)	Far transfer (effect size)	Maintenance effect	Moderators
Karbach and Verhaeghen (2014)	✓ Overal near transfer (0.5)	✓Overall far transfer (0.3)	n.a.	X age X training dose
Mansur-Alves & Saldanha-Silva (2017)[1]	n.a.	✓Raven's (0.09) ✓Bomat (0.24) ✓Cfit (0.24)	✓ Raven's (-0.03) X Cfit Bomat (n/a)	✓ Age ✓ Training intensity X Type of control group ✓ Type of training task X Financial compensation
Melby-Lervåg & Hulme (2013)[1]	✓ Verbal WM (0.8) ✓ Visuospatial WM (0.52)	✓Nonverbal ability (0.20) X verbal abilities ✓Attention (inhibition) (0.32) X Word decoding X Arithmetic	X Verbal WM ✓ Visuospatial WM (0.40) X Nonverbal abilities X Attention X Decoding X Arithmetic	✓ Age (verbal WM) ✓ Intervention type (visuospatial WM; stroop) ✓ Type of control group (non-verbal ability; stroop) ✓ Training dose (stroop) ✓ Design type (stroop) ✓ Learner status (stroop)
Melby-Lervåg, et al. (2016)[1]	✓ Verbal WM (0.31) ✓ Visuospatial WM (0.28)	X Nonverbal abilities ✓Reading comprehension (0.15)	X Nonverbal abilities X Verbal abilities X Word decoding X Reading comprehension ✓ Arithmetic (0.22) X Verbal WM ✓ Visuospatial WM (0.40)	✓ Age (nonverbal ability; verbal WM; visuospatial WM) ✓ Training dose (nonverbal ability; verbal WM; visuospatial WM) ✓ Learner status (nonverbal ability, verbal WM; visuospatial WM) ✓ Intervention programmes (nonverbal ability; verbal WM; visuospatial WM) ✓ Design type (verbal WM; visuospatial WM) ✓ Type of control (nonverbal ability)
Schwaighofer, Fischer, &Bühner (2015) [1,2]	✓ Verbal STM (0.42) ✓ Visuospatial STM (0.61) ✓ Verbal WM (0.3) ✓ Visuospatial WM (0.49)	X Nonverbal ability ✓Verbal ability (0.14) X Wording decoding (0.04) X Mathematicalabilities	✓ Verbal STM (0.27) ✓ Visuospatial STM (0.91) ✓ Visuospatial WM (0.21) ✓ Verbal WM (0.16) X Nonverbal ability (-0.12) X Verbal ability (-0.06) X Wording decoding (0.09) X Mathematical abilities (0.05)	X Age ✓ Training dose (visuospatial STM) ✓ Session duration (verbal STM) X Frequency of training per week X Training interval ✓ Supervision during training (verbal and visuospatial WM) X Instructional support X Feedback ✓ location of the training (visuospatial STM; verbal WM; nonverbal ability) ✓ Intervention type (visuospatial STM; verbal WM; nonverbal ability) ✓ Type of control group (mathematical abilities)
Weicker, Villringer, & Thöne-Otto (2018)[1]	✓ WM functioning (0.60)	✓ Reasoning and intelligence (0.35) ✓ Cognitive control and executive functioning (0.41) ✓ Attention and processing speed (0.39) X Long-term memory X Everyday life functioning and disorders symptoms (0.21)	✓ WM functioning (0.54) ✓ Reasoning and intelligence (0.20) ✓ Cognitive control and executive functioning (0.21) ✓ Attention and processing speed (0.22) X Long-term memory ** ✓ Everyday life functioning and disorders symptoms (0.17)	X Study design X Adaptivity X Improvement in the trained task ✓ Number of sessions (overall WM) X Amount of time spent X Type of intervention (simple and complex span) X Subject group (healthy x clinical)

Note. The values in the parentheses are effect sizes. When comparisons were made separately for active and passive control groups, we selected information regarding the active control group. [1]Information not specific to healthy elderly sample. [2]In this review, studies with participants with more than 75 years were excluded. n.a.- not applicable. The symbol ✓ represents a gain in the outcome while the symbol X represents a non-significant gain.

App. Table 2.

Inclusion and Exclusion Criteria

Inclusion criteria
• Experiments must be randomized controlled trials, or quasi-experimental trials with treatment and either a placebo or a passive control condition tested at pre- and post-intervention.
• Participants must be healthy older adults, without cognitive decline or any type of dementia.
• The intervention of the experimental group must consist of repeated training, computerized or not, focused exclusively on WM skills.
• Presenting average and standard deviation/error for pre- and post-training outcomes.
• Paper had to present an outcome measure following one of the constructs presented in App. Table 6.
Exclusion criteria
• Theoretical and review articles, book chapters, and research protocols.
• Studies conducted with non-human animals.
• Participants with any neurological condition.
• Young participants.
• Training not exclusively targeting WM (e.g., multi-component training/game or training coupled with physical-exercise interventions).
• Active control group with participants performing a WM task. To be included, the active control group must perform a placebo task to facilitate the isolation of the WMT effect in the training group.
• Publications based on the same (or part of a) sample of an experiment already included in the analysis (in this case, the one with more detailed data was kept).
• Absence of pre- and post-training outcomes with average, standard deviation/error and sample size.

App. Table 3.

Characteristics of the Included Studies in Alphabetical Order

Study	Intervention condition (n)	Comparison (n)	Computerized?	Measures/ Outcomes	Number and duration of training sessions	Near gains in posttest	Far gains posttest	Follow-up: time and effect	Completion rate (reason for dropout)
Borella et al. (2010)	CWMS (n = 20)	Questionnaires (n = 20)	X	Cattel test; Stroop; bwd/fwd DS; CWMS; Dot matrix; Pattern comparisons	3x60 min	✓Dot Matrix ✓Fwd/bwd DS	✓Cattell ✓Pattern comparison ✓Stroop test	8 months X all from posttest	100%
Borella et al. (2013)	CWMS (n = 18)	Questionnaires (n = 18)	X	Cattel; Stroop; bwd/fwd DS; CWMS; Dot matrix task; Pattern comparison	3x60 min	✓Fwd DS X Dot Matrix X Bwd DS	✓Stroop incongruent errors X Cattell X Stroop interference index X Pattern comparison	8 months ✓ all from posttest	100%
Borella et al. (2014)	Matrix task (n = 20)	Questionnaires (n = 20)	✓	CWMS; Cattel; Stroop Color; Fwd /bwd Corsi; Pattern comparison.	3x60 min	✓CWMS ✓Fwd/bwd Corsi	✓Pattern comparison X Stroop X Cattell	8 months ✓ CWMS X Fwd/bwd Corsi X Pattern comparison	100%
Borella et al. (2017)	CWMS (n = 18)	Questionnaires (n = 18)	X	LST; The Jigsaw Puzzle test; Fwd/bwd DS; Pattern Comparison; The letter sets	3 x 30 min	X Jigsaw puzzle X LST X DS	✓Pattern Comparison X The letter sets	6 months ✓ Jigsaw Puzzle ✓ LST ✓ Bwd DS X Pattern comparison	n.c.
Bürki et al. (2014)	Verbal N-back (n = 22)	Implicit sequence learning or passive control group (n = 20)	✓	Spatial n-back; Number updating; Reading Span task; RSPM; Stroop; Letter and pattern comparison; Simple reaction time.	10 x 30 min	n.a.	n.a.	n.a	n.c.
Cantarella, Borella, Carretti, Kliegel, & De Beni (2017)	CWMS Task (n = 18)	Questionnaires (n = 18)	X	EPS; TIADL; Cattell; RSPM.	3x 30min	n.a.	✓EPT ✓Cattell ✓RSPM X TIADL	n.a.	100%
Cantarella, Borella, Carretti, Kliegel, Mammarella, et al., 2017 Exp. 1	Matrix task (n = 18)	Questionnaires (n = 17)	✓	CWMS; Fwd/ bwd Corsi span; Pattern comparison task; Cattell	3 x 60 min	X	X	X	n.c.
Cantarella, Borella, Carretti, Kliegel, Mammarella, et al., 2017 Exp. 2	Matrix task (n = 16)	Questionnaires (n = 19)	✓	CWMS, Fwd/Bwd Corsi; Pattern comparison; Cattell.	3 x 60 min	X	X	X	88% (medical issues)
Dahlin, Nyberg, et al. (2008)	Letter/ number/ colors/ spatial location memory task; Keep-track task (n = 13)	PCG (assumed) (n = 16)	✓	Digit symbol substitution; 3-back; Computation span; Recall of concrete nouns; Paired associate learning; Verbal fluency (FAS); RAPM	15 x 45min	✓3-back (for young-old adults) ✓Recall of concrete nouns (for young-old adults) XOther outcomes	X	18 months ✓ 3-back (for young old-group) X Concrete nouns (for young old-group)	86% (reason n.c.)
Du et. al. (2019)	Digit running memory task / chess game (n = 14)	Mental health-related lecture sessions (n = 9)	✓	Running memory task; matrix updating; simple span; complex span; Corsi; Digit Symbol; Number cancellation; Pattern comparison; Association; Recognition; RAPM; Cattell; Paper folding; Spatial relationship; Everyday problems test.	12 x 45 min	✓Color updating ✓Matrix updating X Keep Track X 2-back X Fwd digit span X Corsi block X Corsi spatial span X Operational span	X Processing speed X Episodic memory X Figural reasoning	3 months	70% (hospitalization, moving out of the city)
Goghari et al. (2017)*	Multi-memory game; moving memory game and n-back – BrainGymmer (n = 36)	PCG (n = 29)	✓	Aospan; DS; Tower task; RAPM; Symbol search; Letter fluency; DFT3; TMT-4; CWIT	40 x 30 min	X	X	n.a.	90% (disliking the training, health difficulty, low training dosage)
Guye & von Bastian (2017)	Figural-spatial complex span task / local-recognition task / memory updating task (n=68)	Visual search (n = 74)	✓	Brown-Peterson; binding; memory updating; RAPM; Relationships; Locations; Shifting; Flanker; Stroop; Simon.	25 x 30 min	X	X	n.a.	74% (lack of time, technical problems with: diary, installing software; illness; differences in the assessment protocols pre and post-assessment)

App. Table 3 (cont.)

Heinzel et al. (2013)	N-back (n = 15)	PCG (n = 15)	✓	Fwd/bwd DS; CERAD (Imm recall; Del recall); digit symbol; verbal fluency; RSPM; LPS	12 x 45 min	✓Fwd DS X Bwd DS	✓CERAD del recall ✓Digit symbol X CERAD imm recall X Verbal fluency X RSPM X LPS	n.a.	97% (missing in more than two consecutive training sessions)
Heinzel et al. (2016)	N-back (n = 15)	PCG (n = 14)	✓	Fwd/bwd DS; D2 test, Digit symbol substitution; Verbal fluency; Stroop interference; RSPM; LPS	12 x 45min	X	✓Stroop ✓D2 test ✓LPS X RSPM X DS X Verbal fluency XDigit symbol substitution	n.a.	91% (technical failure during the fMRI scanning)
Lange et al. (2015)	Aospan; dot span; numerical memory updating; figural running; multiple switching (n = 31)	Non-adaptive computerized quizzes and simple board game (n = 31)	✓	Reading span; Swaps; Switching; Numerical running memory span; Berlin intelligence structure test; DS; Word span; Electronic questionnaire for cognitive failures in everyday life; Cognitive failures questionnaire	12 x 60 min	X	X All, except for subjective changes	n.a.	86% (illness or time conflicts)
Payne et al. (2014)	Semantic category span; lexical decision span; sentence reading span (n = 22)	Component control design (n = 18)	✓	Reading span; Sentence listening span; Aospan; Minus-2 span; Sentence memory; Discourse memory; Reading comprehension; Verbal fluency (FAS)	15 x 30 min	✓	✓Verbal fluency ✓Sentence recall X Rivermead X The Nelson-Denny	n.a.	98% (absence in posttest)
Pergher et al., 2018	N-back (n= 14)	PCG (n= 14)	✓	TOVA; Corsi block-tapping test; RAPM	10 x 30 min	X	✓TOVA ✓RAPM	n.a.	100%
Richmond et al. (2011)	Complex WM span task – spatial and verbal subtests (n = 21)	PCG (n = 19)	✓	Reading span; Fwd/bwd DS; RSPM; TEA; CVLT	20 x 20min	✓Reading Span X Fwd/bwd DS	✓CVLT (repetition) X TEA X CVLT (total correct; intrusions)	n.a.	87% (n.c.)
Salminen et al. (2016)	Dual n-back (n = 25)	PCG (n = 21)	✓	WM updating; Task switching; Attentional blink	14 x 35 min	✓VS WM updating X AV WM updating	X Tasking switching X Attentional blink	n.a.	100%
Stepankova et al. (2014)	Verbal n-back (n = 20)	PCG (n = 25)	✓	DS; Letter-number sequencing; Block design (WAIS-III); Matrix reasoning (WAIS-III)	20 x 25 min	✓WM composite score	✓Visuospatial skills composite score	n.a.	100%
von Bastian et al. (2013)	Numerical complex span; figural task switching; tower of frame (n = 27)	Quiz; visual search; counting (n = 30)	✓	Verbal complex span; Kinship integration; Verbal task switching; Binding; n-back; RAPM	20 x 30 min	✓Verbal complex span X Kinship integration	X Biding X Verbal task switching X RAPM	n.a.	(n.c.
Weicker et al. (2018)	WOME intervention (n =20)	PCG (n = 20)	✓	Fwd/bwd DS; Fwd/bwd span board; Spatial addition; Symbol span; PASAT; Stroop; VLMT; LPS-3; TMT-B; TAP (alertness, mental flexibility and go-no-go); Operation Span; N-back	12 x 45min	✓Span board (bwd) X Other WM tasks	X	3 months X	90% (illness, one moved away, car accident, traumatic brain injury, death).
Xin et al. (2014)	Letter, animal, and location running (n = 15)	Computer games (n = 14)	✓	Numerical updating; Fwd/bwd DS; RAPM	20 x 20 min	✓Numerical updating ✓Bwd DS X Fwd DS	X RAPM	n.a.	97% (health problem)
Zinke et al. (2010)	DS fwd/ bcw; Corsi block tapping fwd/bwd and K=ABC icons (n = 20)	PCG (n = 16)	X	RCPM; Stroop color-word interference	10 x 30 min	n.a.	X Stroop X RCPM	n.a.	n.c.

Note. Aospan = Automated Operation Span task; AV WM = auditory-verbal working memory; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CWIT = Color-word Interference Task; CWMS = Categorization Working Memory Span; CVLT = California Verbal Learning Test; DFT3 = Design Fluency Test 3; DS = Digit Span; EPS = Everyday Problem Solving; KAB-Icons = Kaufmann Assessment Battery for Children; LPS = Leistungsprüfsystem; LPS-3 - Leistungsprüfsystem Subtest 3; LST = Listening Span Test; n.a. = Not applicable; n.c.= Not Clear; PCG = Passive Control Group; PASAT = Paced Auditory Serial Addition Test; RAPM = Raven's Advanced Progressive Matrices; RCPM = Raven's Colored Progressive Matrices; RSPM = Raven's Standard Progressive Matrices; RSPM = Raven's Standard Progressive Matrices; TAP = Test of attentional performance; TEA = Test of Everyday attention; TMT = Trail Making Test; TOVA = Test of variables of attention; TIADL = Timed Instrumental Activities of Daily Living; VLMT = Verbal Learning Memory Test; VS WM = visuospatial WM. *These studies also had an active control group. However, they also trained WM or executive function. Therefore, we chose to report data of a control group that was not submitted to a WMT. The symbol ✓ represents a gain in the outcome while the symbol X represents a non-significant gain (except for the column computerized where ✓=yes and X=no.

App. Table 4

Description of the Trained Tasks

Task	Description
CWMS	Participants listen to lists of five-words containing common and animal words. They tap their hand on the table each time they hear an animal word, and they also have to memorize the last word of each list. In the end, participants are prompted to recall the memorized words in serial order.
Chess game	Participants had to listen to a sequence of chess movements and demonstrate, in a 5x5 chess board shown on a computer screen, the final position of the pieces in the correct sequence.
Complex span task – spatial subtest or dot span	Participants are asked to analyze the symmetry of partially filled matrices (or any other interference task) and, at the same time, to encode a sequence of locations on a grid for later recall.
Corsi block-tapping/ span board task	In a wooden board with nine blocks, first the experimenter taps a group of blocks in a specific order, then the participant needs to reproduce the same sequence in fwd or bwd order. The length of the sequence increases until the participant had two consecutive errors in the same level.
Digit Span	Participants listen to a sequence of digits and are instructed to recall them in the fwd or bwd order. The length of the sequence increases until participants have two errors in the same length.
Dual n-back	Participants perform two n-back tasks (visual and auditory) concomitantly. In other words, participants must decide whether the current visual stimulus matches the stimulus N positions back in a sequence presented one by one and, at the same time, they had to decide if the auditory stimulus also matches the one N positions back in the sequence.
Figural task switching	Participants categorize different geometrical shapes following two different rules in an alternate manner. The categorization rule cue is presented simultaneously with the stimuli.
K-ABC Icons	Visuospatial span task, in which participants need to memorize a spatial arrangement of multiple stimuli and then reproduce the icons and their positions on an empty grid after three seconds.
Keep-track task	15 words from various semantic categories are presented in a random order, and participants are asked to mentally place the words into categories (animals, clothes, countries, relatives, sports, professions). In the end, participants are asked to remember the last presented word from each category.
Running task or updating	Lists containing stimuli in a specific order (letter, number, color, animal or spatial location) are presented one by one. The participants are asked to monitor and update the X (e.g., three) last presented stimuli during the list presentation. At the end of the list, participants need to recall them in the correct order.
Lexical decision span task	Participants must classify a set of letters presented one at a time. After a response of the participant, a single letter appears to be later remembered.
Local-recognition task	Participants had to recognize a sequence of stimuli (both color and position) and later recognize if the stimuli are in the correct position and color.
Matrix task	Series of 4 x 4 matrices with white and grey squares are presented. In each series, three black dots appear in different positions in the matrix, one after the other, separated by an empty matrix display. Participants press the space bar whenever a dot occupy a gray cell and, at the end of each series, participants have to recall the position of the last dot seen in an empty matrix.
Memory update task	Participants are presented with colored circles in a 4x4 grid. Later, the circles are presented one at a time and participant have to update its position mentally according to an arrow displayed on the screen (up, down, left or right).
Movie-memory game	Pairs of cards with the same image, but different numbers, are scrambled with only the number visible. Participants pick the two cards with the same image until no cards are left.
Multi-memory game	Participants memorize different tiles placed on a square grid. The tiles disappear and are replaced by a distractor pattern. Participants are then asked to recreate the original pattern. The grid size and tiles' number are adjusted according to the performance.
Multiple switching task	Participants are required to shift attention between number-letter pairs that can be vocal/odd/black or consonant/even/green. A switching cue, such as a red bar moving from one instruction to another or a 10-second countdown, is given to the participants.

App. Table 4 (cont.)

N-back	Participants must decide whether the current stimulus matches the stimulus N positions back in a sequence presented one by one.
Numerical complex span	A sequence of two-digit numbers followed by one digit is presented. Participants judge if the digit is odd or even (concurrent task) and, at the same time, memorize the two-digit number for later free recall in the correct serial order.
Operation span - Aospan	Participants must memorize a list of words while analyzing the veracity of solution of simple equations.
Reading span	Sequences of sentences are presented, and participants are required to make semantic judgments. After a group of sentences, participants recall the last word of each sentence.
Semantic Category Span	Participants make semantic category judgments for series of words. After a set of words, participants recall each word previously categorized in the same order of presentation.
Tower of fame	Participants are asked to imagine a tower with six floors, each one with four apartments. Then they listen sentences describing the location of a famous persons' apartment in this tower. At the end of the task, participants are prompt to recall in which apartment a given famous person lives.
WOME intervention	This training focus on storage (remembering playing cards), selective attention (remembering only the hearts and the diamonds cards), and manipulation (sorting the cards in the same order as seen previously).

Note. CWMS = Categorization Working Memory Span Task; Aospan: = Automated Operation Span Task.

App. Table 5

Description of the Control Tasks

Tasks	Description
Component control design	Participants completed three tasks: semantic categorization; lexical decision; judgment of sentence acceptability. They do not have to recall anything after completing these tasks.
Computer game	Computer games not related to the training task.
Counting	Digits between one and six are presented on a screen. Digits should be repeated in accordance with the presented number. For example, five should appear five times in a row (5 5 5 5 5). If this rule is broken, participants press the wrong number on the keyboard. If all digits are correct, the participant should press zero.
Implicit sequence leaning training	Four squares are presented horizontally and aligned in the center of the screen. One stimulus is pink and the other three grays. The participants respond by pressing the key matching the position of the pink square as fast and accurately as possible.
Mental health-related lectures	Participants attended to mental health-related lecture sessions
Visual search	Participants identify, as fast as possible, a target stimulus and its position within a display of different stimuli. Not all trials have target items and, in this case, the participants should press another key.
Questionnaires	Participants complete questionnaires about different matters (e.g., autobiographic memory; memory sensitivity; psychological well-being, life satisfaction; emotional competencies; coping strategies).
Quiz	General knowledge quiz with multiple choice.
Simple board game	Participants played simple board games such as Ludo.

App. Table 6

Outcome Constructs and Categories Used in the Analysis

Construct Categories	Definition (measures) *Subcategories*
Reasoning	Involves problem-solving (Tests/tasks: Cattel culture fair; figural reasoning; RAPM; RCPM; RSPM; the letter sets; LPS; matrix reasoning WAIS-III). *Cattell; RSPM; RAPM; LPS*
Verbal WM	WM measures using verbal stimuli (Tests/tasks: digit span bwd; categorization working memory span task recall; reading span; verbal complex span; WM updating; letter-number sequencing). *Verbal bwd simple span; verbal complex span; updating.*
Verbal STM	STM using verbal stimuli (Tests/Tasks: fwd digit span). *Verbal fwd simple span*
Visuospatial WM	WM measures with visuospatial stimuli (Tests/tasks: dot matrix task; spatial 2-back; the jigsaw puzzle test; bwd Corsi span; working memory updating performance; bwd span board from WMS-IV) *Visuospatial bwd simple span; visuospatial updating*
Visuospatial STM	STM measure using visuospatial stimuli (Tests/tasks: fwd Corsi task; figural short-term memory; fwd span board from WMS-R) *Visuospatial fwd simple span*

Note. Bwd = backward; Fwd = forward; LPS = Leistungsprüfsystem; RAPM = Raven's Advanced Progressive Matrices; RCPM = Raven's Colored Progressive Matrices; RSPM = Raven's Standard Progressive Matrices; STM = Short-term Memory; WAIS-III = Wechsler Adult Intelligence Scale - III; WM = Working memory; WMS = Wechsler Memory Scale; WMS-IV = Wechsler Memory Scale-IV.

App. Table 7

Description of the Tasks Used to Assess Near and Far Transfer

Tasks (cognitive domain)	Description of the task
NEAR TRANSFER	
Binding	Sequences of stimuli (e.g., words or shapes) are displayed in different positions on the screen. The stimuli are again displayed, and the participants judge if they are in the same position or not.
Brown-Peterson	Participants have to memorize a series of Gabor patches, followed by a distractor task.
CWMS	See App. table 4 for a detailed description.
Category fluency	During a given time, participants are asked to say as many words as possible from a specific category.
Computation span	Participants solve arithmetic problems while holding the final digit from each problem in memory for later recall.
Corsi block tapping/ span board task	See App. table 4 for a detailed description.
Corsi spatial span	Du et al. (2018) modified the Corsi task by presenting a flag inside each block and requiring the participants to identify orientation of the flag. Subsequently, participants have to recall the location of the blocks.
Digit Span	See App. table 4 for a detailed description.
Discourse memory	Participants are required to read a whole paragraph and then to reproduce it as accurately as possible.
D2 test	Participants are asked to cross out any letter 'd' with two marks above or below it. The other presented stimuli are distractors and should not be marked.
Digit symbol substitution	Participants complete as fast and accurately as possible digit-symbol correspondences during a specific time, following a key provided in the top of the page.
Dot matrix	Participants see a sequence of dots displayed in different locations in a 5 × 5 grid interspersed with equations. At the end of the display, they should point, in a 5 × 5 blank grid, the exact spatial locations of the dots as presented previously.
Keep track measure	Participants see a list of words from four different categories, and they need to recall the most recent words from each category
Kinship integration	Descriptions of the kinship between two people are presented sequentially. Afterward, participants indicate the relationship between two people, which is not explicitly mentioned in the descriptions, but could be inferred from the presented information.
Letter-number sequencing	Participants listen to a mixed sequence of number and letters, and they are asked to recall the sequence items by ordering first the numbers and then the letters in the ascending order.
Memory updating	Participants have to memorize the orientation of arrays and then update their orientation by rotating them according to an arrow indicating the rotation direction.
Minus-2 span	After listening to a sequence of digits, participants are instructed to subtract two from each number and then produce the obtained sequence.
N-back task	See App. table 4 for a detailed description.
Operation span - Aospan	See App. table 4 for a detailed description.
Reading span	See App. table 4 for a detailed description.
Recall of concrete nouns	Participants must freely recall a list of 18 nouns read by the experimenter. There are two subsequent trials in which items not recalled are re-read. Participants are required to remember all the items on the list.
Sentence span	After listening to a series of sentences with a variable number of words, participants do a free recall test and retrieve the maximum number of sentences they can.
Symbol span – WMS	Participants are presented with a row of symbols. Then, they recognize these symbols in the correct order in a set of symbols.
Swaps	Three letters are presented simultaneously on the computer screen. Participants mentally swap the position of two letters as many times as requested. In the end, after conducting all swaps, participants type the three letters in the expected order.
The Jigsaw puzzle	Participants solve puzzles of inanimate objects. However, they must be done without moving the pieces. Instead, participants indicate where each piece should be moved. The level of difficulty is adapted by manipulating the number of puzzle pieces.
Updating / running tasks	A series of stimuli are presented, and participants are asked to recall the three last numbers presented in the correct serial order.
Verbal complex span	A sequence of words followed by one letter is presented to the participants. They evaluate if the letter is a consonant or a vowel and memorize the words for later free recall in the expected serial order.
WMS Spatial addition	Participants are presented with a grid with dots located in different positions in two separate pages. Participants add or subtract the locations of the dots, holding and manipulating visuospatial information.

App. Table 7 (cont.)

Word span	Participants listen to a sequence of words, and they are required to recall them in the same serial order.
FAR TRANSFER	
Attentional Blink	A stream of letters and digits are displayed one by one on a screen. Participants identify a first visual digit followed by a second auditory digit.
Berlin intelligence structure test	Intelligence test covering the following domains: verbal; numeric; spatial; processing capacity; creativity; memory; speed.
Block design	Participants reproduce a model using red-and-white blocks in a given time.
Cattell test	It contains four subtests: 1) participants see an incomplete series of abstract shapes and figures, and they must choose the one that best fits the series from six options. 2) participants see 14 problems comprising abstract shapes and figures, and they must choose which two out of five differ from the other three. 3) 13 incomplete matrices containing four to nine boxes of abstract figures and shapes plus an empty box are presented. Participants must select the best fitting option from six possible alternatives; 4) 10 sets of abstract figures, lines, and a single dot are shown to the participants, along with five alternatives. Participants assess the relationship between the figures and choose the best fitting option.
CERAD immediate and Delayed Recall	Participants are asked to free recall ten words presented on printed cards. There are three learning trials in which the words are presented in different orders. Participants recall the learned items after each trial immediately and with a delayed interval of 15 minutes.
CFQ	A self-report questionnaire with 32 items that evaluates perception, memory, and motor function in everyday life.
CVLT	Participants are asked to free recall a 16-word list. This list is repeated five times or until participants recall all the words. After that, an intrusion list is presented to recall. Delayed recall is also assessed after 20 minutes.
CWIT	These are two subtests of the DKEFS, one that measures inhibition control (Stroop effect), and other that measures cognitive flexibility (switching between inhibitory and non-inhibitory responses).
DF	It is a subtest from the DKEFS in which participants are instructed to draw as many designs as possible by connecting five dots. Some dots are filled, while others are not. Participants must alternate between filled and unfilled dots.
Digit symbol	Participants are presented to nine numbers associated with symbols. Then they have to fulfill, as fast as possible, a sequence of number with their respective symbol.
eKFA	It is a 13-items questionnaire of daily cognitive failures.
EPS	Hypothetical real-life situations questionnaire.
Flanker	Participants indicate the orientation of a central arrow presented between two other arrows or two other stimuli.
LST	Participants listen to sets of simple sentences and judge its plausibility. Later, they recall the last word of each sentence.
Letter and pattern comparison	Two pages containing one column of 30 items are presented, and participants decide whether the arrangements are identical or not.
LPS	Participants are asked to analyse patterns of symbols and to mark the one that does not match the pattern.
Locations	Participants have to identify the rule of a spatial distribution of a x in four lines. Then they place a 'x' in a new line according to the rule previously identified.
Matrix reasoning	Participants select the best fitting response to complete a missed element in a matrix.
Memory association	Participants learn and remember the relationship between two unrelated items.
Memory recognition	Participants had to recognize previously learned items (meaningless-images and words)
Number Cancellation	Participants are presented with lines having different digits. They have to cross off, as fast as possible, two specific digits presented on the top of the form.
Paired-associate learning	Participants are asked to learn word pairs. After studying a list of 18 pairs, when given the first word of the pair as a cue, participants are asked to recall the corresponding word from the pair.
Paper folding	Participants have to do, mentally, a sequence of steps related to the action of folding a paper, and then recognize the pattern that corresponds to the outcome of the previous folding steps.
Pattern comparison	Participants check if two figures presented side-by-side are the same or not, as fast as possible.
RAPM; RCPM; RSPM	By choosing from six to eight options, participants are asked to complete a missing part from a figure composed of lines and shapes.
Reading comprehension	Participants read prose passages and then answer questions about it.
Relationships	Participants identify the correct Venn diagram representing the relationship among three stimuli.
Shifting	It is a shifting task, in which participants categorize a stimulus according to two different classification rules.
Simon	Participants indicate the color of a stimulus presented on the left, right or in the center of the screen by pressing an arrow key congruent, incongruent or neutral to the stimulus position.
Simple reaction time	Participants press a button box as quickly as possible when a cross is displayed in one of five positions on a black screen.
Spatial relationship	Reasoning test, in which participants have to rotate objects mentally.

App. Table 7 (cont.)

Stroop task	It is a task that contains a congruent condition wherein colour names are presented in congruent ink colour and an incongruent condition in which colour names are printed in incongruent ink colour. A third control condition is presented, containing colour patches. Participants are instructed to say the ink colour of each stimulus.
Switching	Participants switch between different instructions, and the switch is prompted by specific cues.
Symbol search	In each trial, individuals are required to check if at least one of two symbols initially presented can be found amid a sequence of other symbols. If they can find at least one corresponding symbol, they draw a cross in yes, otherwise they signal the answer no. They have 120 seconds to complete the task.
TAP alertness	Participants see a series of stimulus and give a response when: a specific stimulus is presented or a specific cue precedes a stimulus.
TAP mental flexibility	Participants are simultaneously presented with a letter and a number on random sides of a screen. They have to press a key on the side where the letter or the number is displayed.
TAP go-no-go	Participants are randomly presented with two different stimuli, they have to press a key, as fast as possible, when the target is shown, while suppressing the response to the non-target stimuli.
TEA	Subtests that cover selective attention, sustained attention, and attentional switching.
The letter sets	Participants identify a set of letters that deviates from a pattern.
TIAD	Participants simulate the actions involved in different activities: communication; use of money; cooking; shopping; use of medicine.
TMT	Participants connect numbers or letters in ascending order or alternate between numbers and letters. In the DKEFS version, they had also to connect dots to assess motor speed.
TOVA	In this test participants have to respond to a target that is shown first in an infrequent condition and later in a more frequent condition.
Tower Task (DKEFS)	Participants build series of towers with five coloured disks using an apparatus with three-pegs varying in size. The aim is to complete a tower like the one presented in a picture model, using the least number of movements.
Verbal fluency	Letter fluency: participants are asked to produce as many words as possible beginning with the letters F, A, and S during 90 s, excluding proper names and places. Category fluency: participants are asked to say the maximum of words as possible about specific categories and by complying to specific constraints, such as provisions, animal names beginning with the letter S, and professions beginning with the letter B.
VLMT	Participants are asked to free recall a word list read by the experimenter. The list is repeated five times. After that, an intrusion list is presented to recall. Delayed recall, after 20 minutes, is also performed. In the end, a list containing all the words and distractors is shown to the participants, and they are required to recognize the words from the first list.

Note. CFQ = Cognitive Failures Questionnaire; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CWIT = Colour-word interference task; CWMS = Categorization Working Memory Span Task; CVLT = California Verbal Learning Test; DFT = Design Fluency YRDY; DKEFS = Delis-Kaplan Executive Function System; eKFA = electronic Questionnaire for Cognitive Failures in Everyday Life; EPS = Everyday problem solving; RAPM = Raven's Advanced Progressive Matrices; RSPM = Raven's Standard Progressive Matrices; LSP = Leistungsprüfsystem; LST = Listening Span Test; TEA = Test of Everyday Attention; TIAD = Timed Instrumental Activities of Daily Living; TMT = Trail Making Test; TOVA = Test of Variables of Attention; VLMT = Verbal Learning Memory Test.

App. Table 8
Influential Studies in Each Group (Divided by Measure)

	Construct Measure	Influential Study	Outcome Id	Final No. of experiments	Final No. Outcomes
POSTTEST	**Reasoning**				
	Cattell	No		8	8
	RSPM	7 – Cantarella et al., 2016 19 – Richmond et al., 2011	8 28	4	4
	RAPM	13 – Guye & von Bastian, 2017	17	5	5
	LPS	NA		3	3
	Others			6	14
	Total	13 – Guye & von Bastian, 2017	18	25	33
	Verbal WM				
	Bwd Simple span	1 – Borella et al., 2010	38	9	9
	Complex span	3 – Borella et al., 2014 – Exp1	40	13	16
	Updating	25 – Xin et al., 2014	80, 81	7	11
	Others			3	4
	Total			20	41
	Visuospatial WM				
	Bwd Simple span	3 – Borella et al., 2014 – Exp1	84	4	4
	Updating	11 – Du et al., 2018 13 – Guye & von Bastian, 2017	90 94	4	4
	Others			4	5
	Total	1 – Borella et al., 2010	82	10	13
	Verbal STM				
	Simple Span	1 – Borella et al., 2010	99	11	12
	Visuospatial STM				
	Simple span	3 – Borella et al., 2014 – Exp1	112	5	6
FOLLOW-UP	**Reasoning**				
	Cattell	11 – Du et al., 2018	128	6	6
	Others			4	6
	Total			10	12
	Verbal WM				
	Bwd Simple span	24 – Weicker et al., 2018	146	4	4
	Complex span	3 – Borella et al., 2014 – Exp1	134	7	7
	Updating	NA		3	6
	Total			9	17
	Visuospatial WM				
	Bwd Simple span	3 – Borella et al., 2014 – Exp1	153	5	5
	Updating	NA		2	3
	Others			3	3
	Total			8	11
	Verbal STM				
	Simple span	NA		6	6
	Visuospatial STM				
	Simple span	NA		5	6
	TOTAL			27	156

Note. NA – Not applicable due to the existence of a small number (< 4) of experiments in the group (measure). Influential studies indicate the studies that are outliers and have strong influence in the results. These studies were excluded from the analysis.

App. Table *9*

Sensitivity Analysis to Assess Publication Bias and "Small-Studies Effects"

	Construct Measure	N. effects	N. studies	Publication bias			Random-effect model mean effect				Fixed-effect model mean effect				RE – FE differ.	Higher order Likelihood inference	
				Leave-one-out	Trim&Fill	Assym. Tests	Estimate	95% CI	*p*-value	RVE p-value	Estimate	*p*-value	95% CI	HC 95% CI		Estimate	Skovgaard's *p*-value
POSTTEST	Reasoning																
	Cattell	8	8	No	NA	NA	0.40	[0.15, 0.66]	<.002 **	.02 *	0.40	.002 **	[0.15, 0.65]	[0.16, 0.64]	<0.01	0.40	.02*
	RAPM	5	5	No	NA	NA	-0.19	[-0.47, 0.09]	.18	.17	-0.19	.18	[-0.47, 0.09]	[-0.45, 0.07]	<0.01	-0.19	.67
	RSPM	4	4	No	NA	NA	0.10	[-0.21, 0.41]	.52	.09	0.1	0.52	[-0.21, 0.41]	[-0.19, 0.39]	<0.01	0.10	.10
	Verbal WM																
	Bwd simple span	9	9	No	Yes	NA	0.18	[-0.11, 0.48]	.22	.26	0.16	.15	[-0.06, 0.38]	[-0.17, 0.49]	0.02	0.18	.24
	Complex span	16	13	No	No	No	0.34	[0.09, 0.58]	.007 **	.02*	0.31	<.001***	[0.14, 0.49]	NA	0.03	NA	NA
	Updating	11	7	No	NA	NA	-0.06	[-0.27, 0.16]	.60	.55	-0.06	.60	[-0.27, 0.16]	NA	<0.01	NA	NA
	Visuospatial WM																
	Bwd simple span	5	5	No	NA	NA	0.17	[-0.30, 0.65]	.47	.51	0.17	.28	[-0.14, 0.48]	[-0.40, 0.74]	<0.01	0.17	.50
	Updating	4	4	No	NA	NA	0.50	[0.16, 0.83]	.004**	.02*	.50	.004**	[0.16, 0.83]	[0.18, 0.81]	<0.01	0.50	.04*
	Verbal STM																
	Simple span	12	11	-12 sig	Yes	Yes	0.16	[-0.04, 0.36]	.13	.16	0.15	.12	[-0.04, 0.34]	NA	0.01	NA	NA
	Visuospatial STM																
	Simple span	6	5	No	NA	NA	-0.03	[-0.39, 0.32]	.86	.74	-0.01	.96	[-0.28, 0.27]	NA	0.02	NA	NA
FOLLOW-UP	Reasoning																
	Cattell	6	6	-3,-4 sig	NA	NA	0.24	[-0.03, 0.51]	.08	.13	0.24	0.08	[-0.03, 0.51]	[-0.01, 0.49]	<0.01	0.24	.14
	Verbal WM																
	Bwd simple span	4	4	No	NA	NA	0.16	[-0.17, 0.50]	0.35	.19	0.16	0.35	[-0.17, 0.50]	[-0.15, 0.48]	<0.01	0.16	.03 *
	Complex span	7	7	-4,5,9 nonsig.	NA	NA	0.36	[0.03, 0.68]	.03*	.07	0.35	.009 **	[0.09, 0.62]	[0.01, 0.70]	0.01	0.35	.07
	Updating	6	3	No	NA	NA	-0.12	[-0.50, 0.24]	.50	.44	-0.13	050	[-.050, 0.24]	NA	<0.01	NA	NA
	Visuospatial WM																
	Bwd simple span	5	5	No	NA	NA	0.05	[-0.25, 0.35]	.75	.72	0.05	.75	[-0.25, 0.35]	[-0.23, 0.33]	<0.01	0.05	.89
	Verbal STM																
	Simple span	6	6	No	NA	NA	0.18	[-0.10, 0.45]	.21	.19	0.18	.21	[-0.10, 0.45]	[-0.08, 0.44]	<0.01	0.18	.98
	Visuospatial STM																
	Simple span	6	5	No	NA	NA	-0.04	[-0.33, 0.24]	.76	.72	-0.04	.76	[-0.33, 0.24]	NA	<0.01	NA	NA

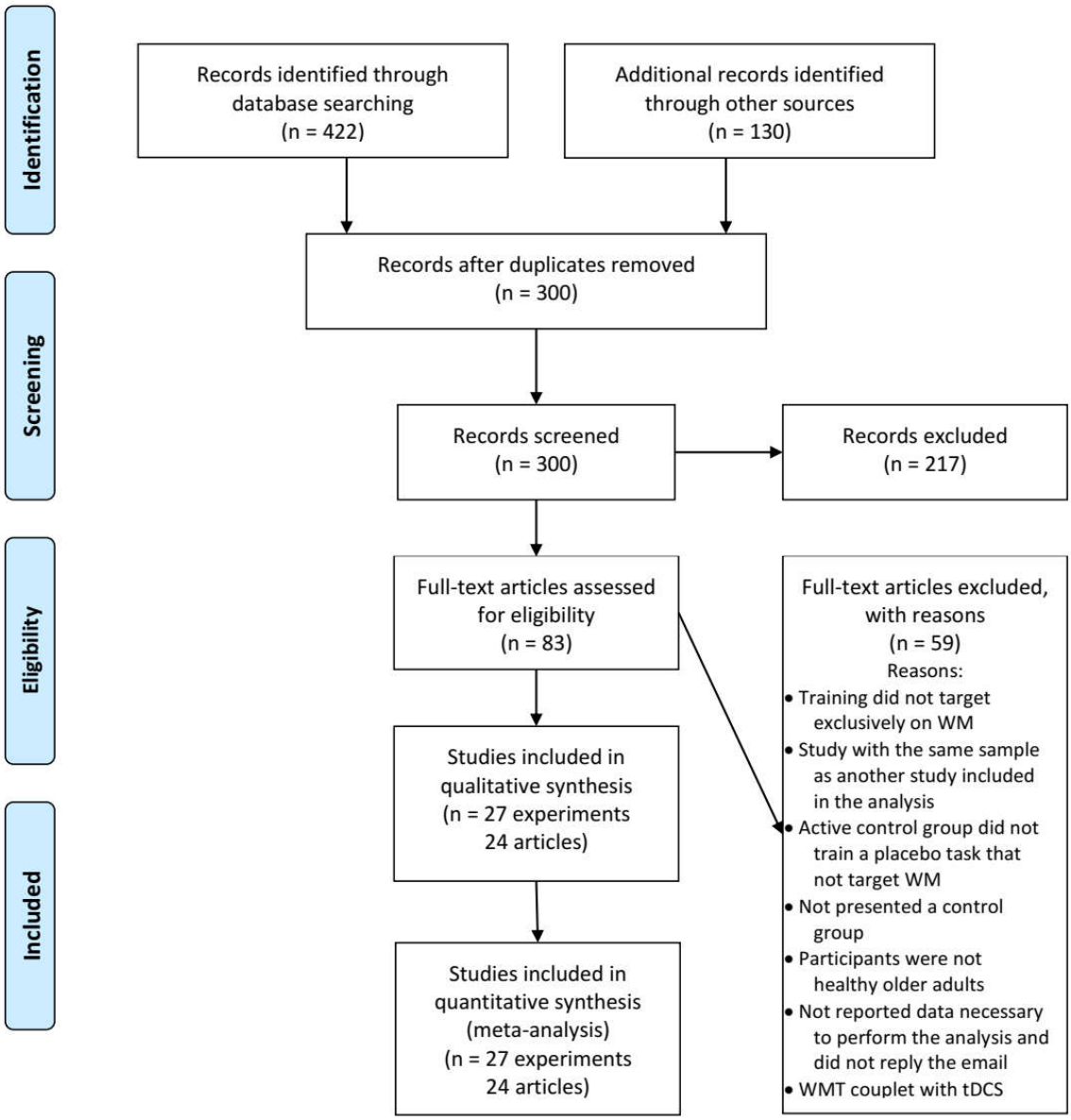
Note. ^p<0.1, *p<0.05, **p<0.01, ***p<0.001. Bwd – Backward. HC – Henmi and Copas method. RE – FE differ. – the difference between Random-effect model meand effect and Fixed-effect model mean effect. RVE – Robust Variance Estimation. Higher order Likelihood inference method described in Guolo and Varin (2017), corrects for small number of studies. Sensitivity analysis of the four methods (Fixed effect-modeling; Hemni and Copas; Multilevel modeling and the Higher order likelihood inference method) did not differ significantly, showing no problem with small-studies effects. In the leave-one out column, *sig* means that when we take out the indicated study, the effect becomes significant; *nonsig* is the opposite, when we take out the indicated study, the effect becomes non-significant; *No* in leave-one-out column means no issues in this analysis.

App. Table 10

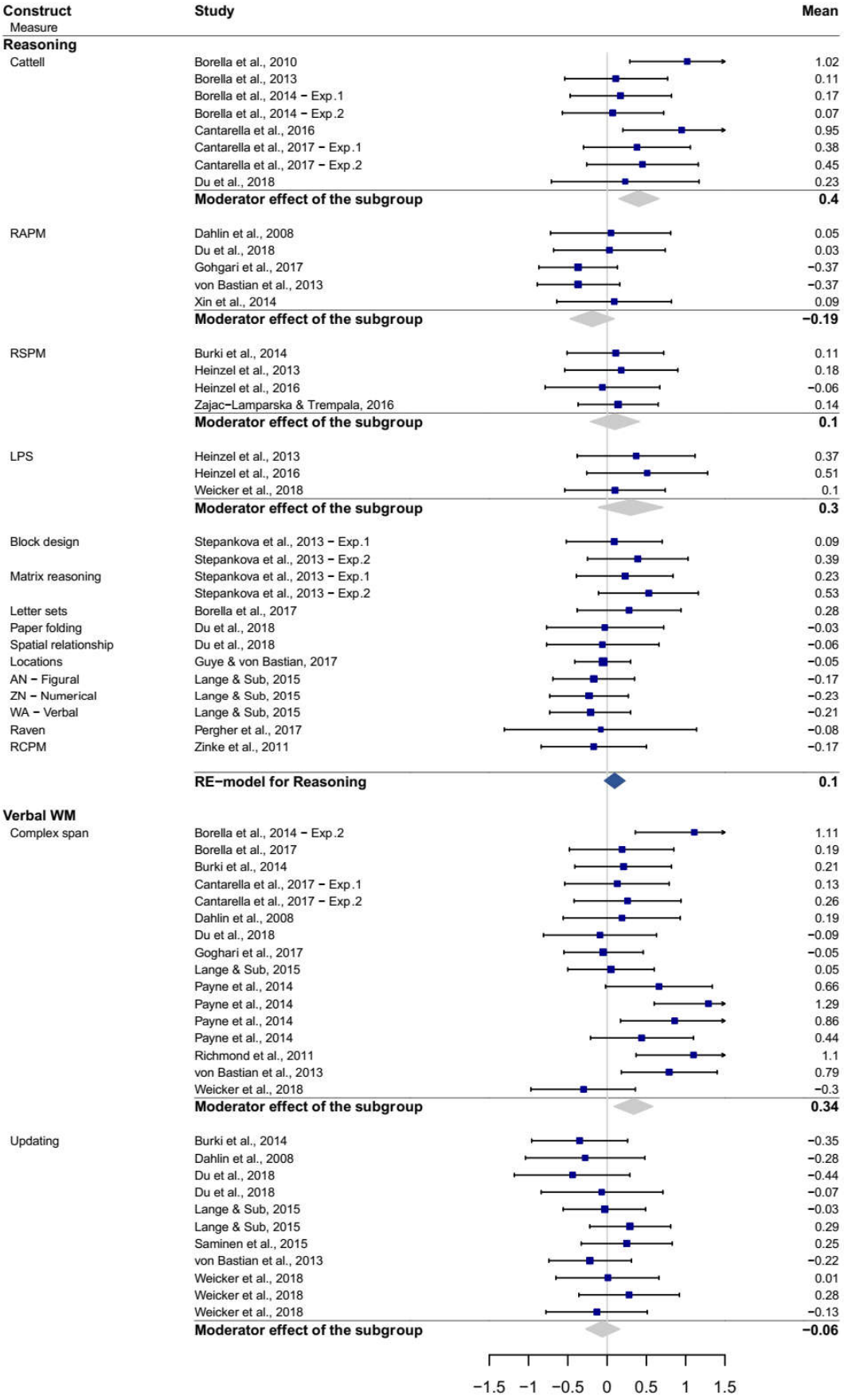
Moderation Analysis of Control Group Type

	Construct	Estimate	SE	95% CI	p-value
Immediate Posttest	Reasoning	-0.04	0.14	[-0.32, 0.23]	.77
	Verbal WM	-0.05	0.17	[-0.39, 0.29]	.78
	Visuospatial WM	0.54	0.24	[0.75, 1.00]	.02*
	Verbal STM	-0.01	0.22	[-0.45, 0.43]	.96
	Visuospatial STM	-0.26	0.43	[-1.09, 0.58]	.55
Follow-up	Reasoning	0.05	0.30	[-0.55, 0.64]	.88
	Verbal WM	-0.23	0.27	[-0.76, 0.31]	.41
	Visuospatial WM	0.03	0.32	[-0.60, 0.65]	.93
	Verbal STM	-0.32	0.30	[-0.91, 0.27]	.28
	Visuospatial STM	-0.14	0.35	[-0.83, 0.56]	.70

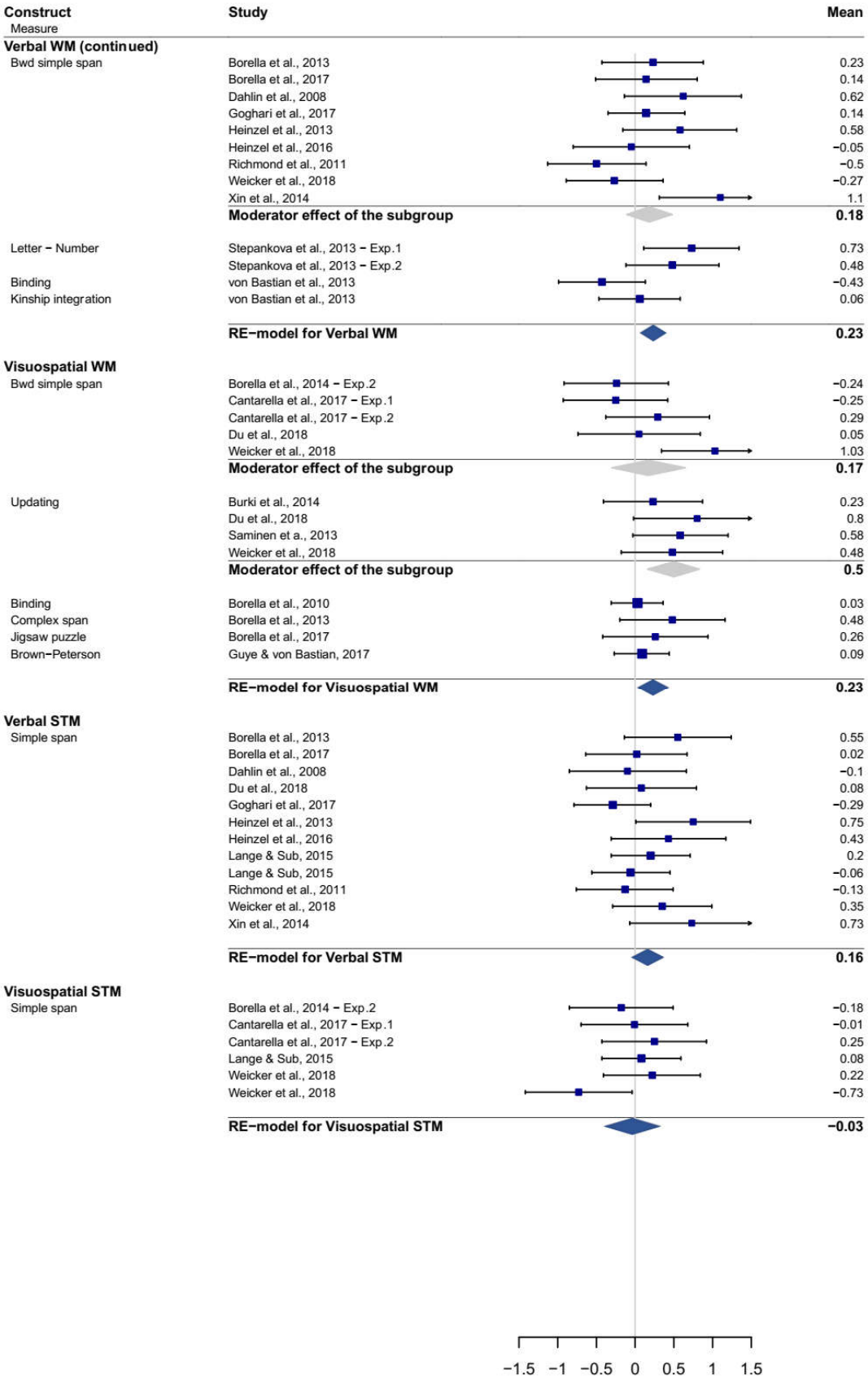
Note. $*p < .05$.



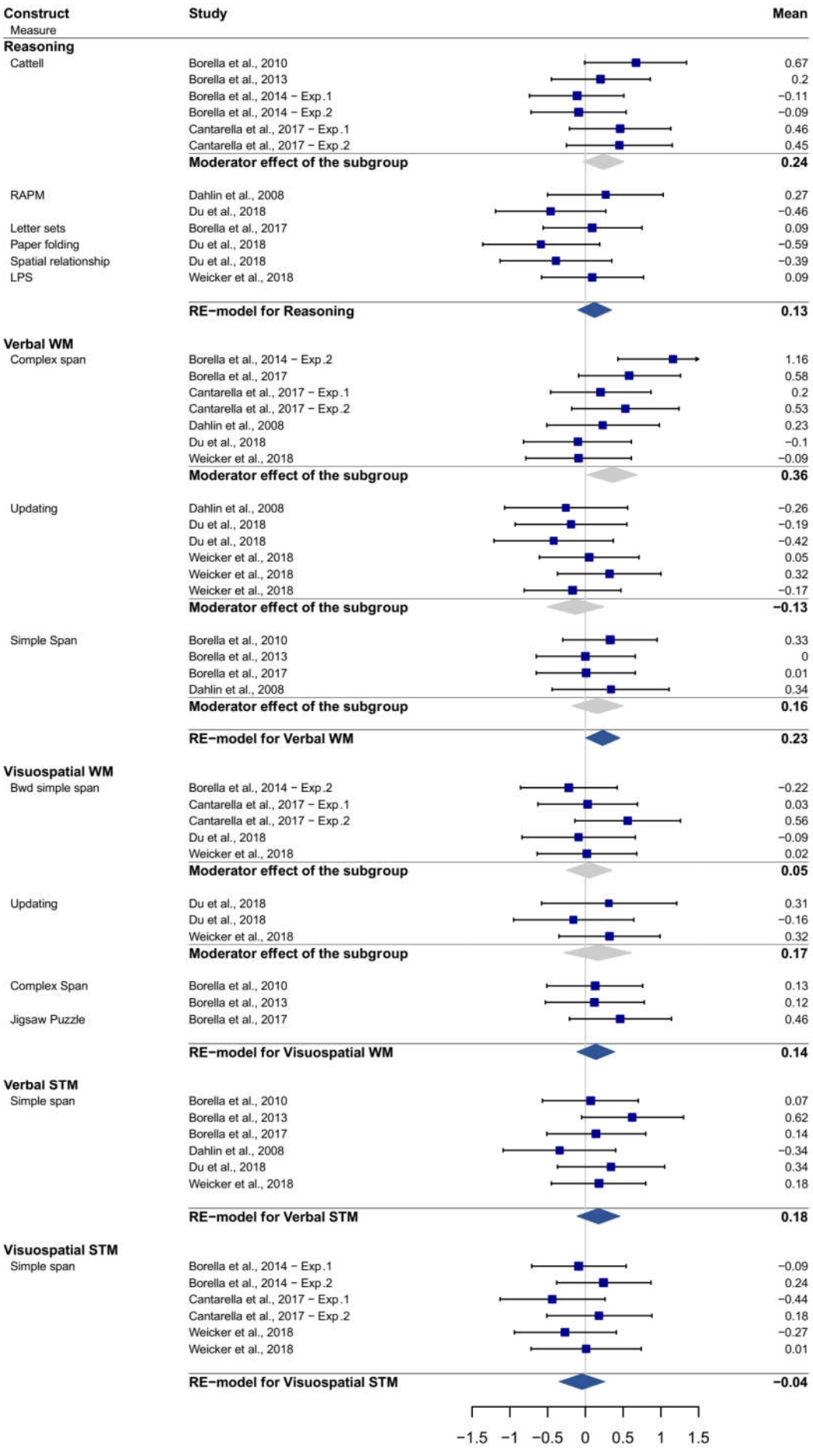
App. Figure 1. PRISMA flow diagram.



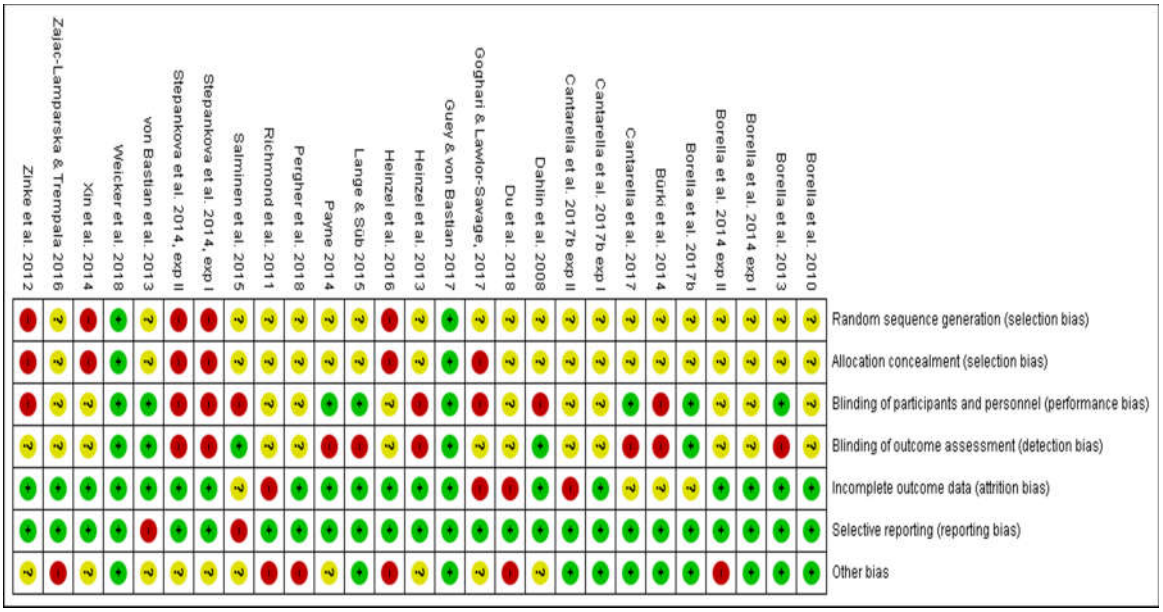
App. Figure2. Posttest Forest plots. *Note.* Pooled effect size for subcategories (grey diamond) and constructs (blue diamond).



App. Figure2 (cont.)



App. Figure 2 (cont.). Follow-up Forest plots.



App. Figure 3. Risk of bias summary graph. Rows correspond to the articles included in the meta-analysis, and each column corresponds to the risk of bias assessment items. Each circle represents the risk of bias assessment a particular parameter in each study: +low risk; - high risk; ?unclear.

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APPENDIX A

Supplementary material (study I)

Table A

Combinations of the Descriptors Used in the Literature Search (January 16, 2019)

Database(s)	Combination of descriptors	Field search
Web of Science (Scielo)	(training) AND ("working memory") AND ("old* adult*")	TOPIC (Title, abstract, author keywords, keywords plus)
Scopus	(training) AND ("working memory") AND ("old* adult*"))	Abstract
Pubmed	Training AND "Working memory" AND ("old* adults")	Title/abstract
PsycINFO, PsycARTICLES	(Training) AND ("working memory") AND ("old* adult*")	Abstract
Science Direct	(Training AND "Working memory" AND ("older adults")	Title, abstract, keywords

Table B

References of the Included Studies

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Table C

Sensitive Analysis - Posttest

Construct	r	ρ	RVE mean				Q-test	σ^2_1	σ^2_2
			Estimate	95% CI	*p*value	RVE p-value			
		.3	.097	[-.041, .234]	.1676	.165	21.19	<.01	<01
	.3	.5	.098	[-.043, .239]	.1734	.160	21.29	<.01	<.01
		.7	.097	[-.047, .242]	.1856	.165	22.51	<.01	<.01
		.3	.105	[-.023, .234]	.1087	.125	28.40	.01	<.01
Reasoning	.5	.5	.103	[-.026, .233]	.1175	.134	28.53	.01	<.01
		.7	.100	[-.030, .231]	.1316	.148	30.18	.01	<.01
		.3	.119	[-.006, .245]	.0627 ^	.0766 ^	43.27 ^	.04	<.01
	.7	.5	.118	[-.009, .245]	.0694 ^	.0834 ^	43.46 ^	.04	<.01
		.7	.114	[-.014, .242]	.0816 ^	.0958 ^	46.02 ^	.04	<.01
		.3	.223	[.065, .380]	.0055 **	.0115 *	55.06 *	<.01	.05
	.3	.5	.233	[.058, .408]	.0090 **	.0078 **	66.26 **	<.01	.07
		.7	.240	[.049, .432]	.0137 *	.0062 **	96.23 ***	<.01	.10
		.3	.223	[.069, .377]	.0045 **	.0122 *	73.77 ***	<.01	.08
Verbal WM	.5	.5	.228	[.065, .392]	.0062 **	.0095 **	88.79 ***	<.01	.09
		.7	.235	[.059, .411]	.0090 **	.0075 **	128.94 ***	<.01	.11
		.3	.228	[.072, .384]	.0042 **	.0114 *	112.21 ***	.02	.10
	.7	.5	.225	[.070, .379]	.0045 **	.0119 *	135.06 ***	<.01	.12
		.7	.227	[.067, .388]	.0055 **	.0103 *	196.02 ***	<.01	.13
		.3	.223	[.016, .431]	.0345 *	.0879 ^	11.29	<.01	<.01
	.3	.5	.214	[.008, .419]	.0414 *	.0929 ^	12.02	<.01	<.01
		.7	.220	[-.006, .445]	.0564 *	.0725 ^	14.55	<.01	.02
		.3	.228	[.035, .441]	.0215 *	.0564 ^	15.10	.02	<.01
Visuospatial WM	.5	.5	.228	[.029, .426]	.0245 *	.0619 ^	16.03	.02	<.01
		.7	.232	[.013, .450]	.0379 *	.0592 ^	19.33	<.01	.04
		.3	.247	[.047, .446]	.0154 *	.0407 *	22.85 *	.04	<.01
	.7	.5	.247	[.044, .450]	.0173 *	.0463 *	24.16 *	.01	.05
		.7	.245	[.035, .454]	.0223 *	.0488 *	28.88 **	<.01	.07
		.3	.151	[-.070, .371]	.1798	.181	8.84	<.01	<.01
	.3	.5	.153	[-.070, .376]	.1797	.184	9.03	<.01	<.01
		.7	.155	[-.072, .382]	.1801	.185	9.50	<.01	<.01
		.3	.159	[-.045, .362]	.1257	.161	12.15	.02	<.01
Verbal STM	.5	.5	.159	[-.045, .363]	.1258	.161	12.41	<.01	.01
		.7	.162	[-.046, .369]	.1269	.158	13.06	<.01	.02
		.3	.179	[-.024, .382]	.0846 ^	.117	19.41 ^	.04	.01
	.7	.5	.179	[-.024, .382]	.0846 ^	.117	19.85 ^	.03	.02
		.7	.179	[-.024, .382]	.0846 ^	.117	20.92 *	.02	.03
		.3	-.030	[-.366, .306]	.8596	.746	5.22	<.01	.02
	.3	.5	-.030	[-.410, .351]	.8782	.750	6.76	<.01	.06
		.7	-.029	[-.448, .389]	.8912	.755	10.46 ^	<.01	.10
		.3	-.033	[-.354, .288]	.8408	.729	6.99	<.01	.05
Visuospatial STM	.5	.5	-.032	[-.388, .324]	.8619	.739	9.06	<.01	.08
		.7	-.031	[-.417, .356]	.8764	.746	14.00 *	<.01	.11
		.3	-.036	[-.341, .269]	.8181	.713	10.61 ^	<.01	.07
	.7	.5	-.034	[-.363, .295]	.8391	.725	13.73 *	<.01	.09
		.7	-.033	[-.383, .318]	.8543	.733	21.28 ***	<.01	.11

Note. ^p<.1, *p<.05, **p<.01, ***p<.001. NA = Not Applicable (only for groups from the same measure); I^2 – total heterogeneity / total variability; τ^2 – estimated amount of total heterogeneity; σ^2_1 – Variance component of the 3-level model for the between-studies heterogeneity; σ^2_2 – Variance component of the 3-level model for the within-studies heterogeneity; RVE = Robust Variance Estimation; WM = Working Memory. This table represents the sensitivity analysis performed with three different correlational values (r = 0.3, 0.5, 0.7 and ρ=0.3, 0.5, 0.7) due to the fact that correlations between pre-and post-test scores and between-studies were not reported in the original studies. r is the pre-posttest correlation and ρ is the intra-study measures correlation. Results are consistent between the different correlations.

Table C (cont.)

Sensitive Analysis - Follow-up

Construct	r	rho	Estimate	95% CI	RVE mean p-value	Skovgaard's p-value	RVE p-value	Q-test	τ^2	$\sigma^2{}_1$	$\sigma^2{}_2$
		.3	.113	[-.129, .355]	.3612		.383	7.54		<.01	<.01
	-3	.5	.130	[-.115, .376]	.2979		.276	6.90		<.01	<.01
		.7	.143	[-.105, .391]	.2583		.210	6.54		<.01	<.01
		.3	.121	[-.108, .349]	.2997		.331	10.22		.02	<.01
Reasoning	.5	.5	.131	[-.085, .347]	.2355		.268	9.36		.01	<.01
		.7	.142	[-.070, .353]	.1891		.209	8.86		<.01	<.01
		.3	.131	[-.086, .349]	.2373		.270	15.92		.05	<.01
	.7	.5	.138	[-.072, .347]	.1972		.230	11.58		.04	<.01
		.7	.145	[-.057, .346]	.1596		.194	13.76		.03	<.01
		.3	.209	[-.022, .439]	.0760 ^		.105	12.80		<.01	<.01
	.3	.5	.232	[-.012, .477]	.0626 ^		.083 ^	13.97		<.01	<.01
		.7	.248	[-.015, .510]	.0640 ^		.073 ^	17.58 *		<.01	.01
		.3	.218	[-.005, .440]	.0553 ^		.092 ^	16.99		.02	<.01
Verbal WM	.5	.5	.231	[.006, .457]	.0446 *		.079 ^	18.59		.01	.01
		.7	.237	[.001, .476]	.0491 *		.075 ^	23.46		<.01	.03
		.3	.225	[.002, .448]	.0481 *		.083 ^	25.39 ^		.05	.01
	.7	.5	.226	[.004, .448]	.0461 *		.081 ^	27.89 *		.03	.03
		.7	.227	[.006, .449]	.0443 *		.079 ^	35.43 **		.01	.04
		.3	.140	[-.012, .400]	.2915		.124	4.01		<.01	<.01
	.3	.5	.142	[-.126, .409]	.2990		.134	4.48		<.01	<.01
		.7	.140	[-.133, .413]	.3147		.152	5.61		<.01	<.01
		.3	.139	[-.084, .361]	.2228		.129	5.43		<.01	<.01
Visuospatial WM	.5	.5	.140	[-.089, .368]	.2313		.140	6.04		<.01	<.01
		.7	.137	[-.096, .370]	.2500		.137	7.53		<.01	<.01
		.3	.136	[-.041, .313]	.1332		.137	8.43		<.01	<.01
	.7	.5	.136	[-.046, .317]	.1423		.151	9.33		<.01	<.01
		.7	.136	[-.064, .335]	.1832		.160	11.51		<.01	.01
	.3	-	.178	[-.145, .501]	.2804	.2102	.187	2.79	<.01		
Verbal STM	.5	-	.178	[-.097, .452]	.2048	.9828	.186	3.85	<.01		
	.7	-	.176	[-.053, .405]	.1317	.2476	.189	6.20	.01		
		.3	-.048	[-.380, .284]	.7787		.689	2.20		<.01	<.01
	.3	.5	-.045	[-.383, .293]	.7926		.711	2.32		<.01	<.01
		.7	-.045	[-.387, .298]	.7977		.721	2.62		<.01	<.01
		.3	-.046	[-.331, .238]	.7488		.698	3.01		<.01	<.01
Visuospatial STM	.5	.5	-.044	[-.334, .245]	.7632		.718	3.17		<.01	<.01
		.7	-.045	[-.338, .249]	.7661		.726	3.57		<.01	<.01
		.3	-.044	[-.270, .183]	.7053		.719	4.75		<.01	<.01
	.7	.5	-.043	[-.276, .191]	.7211		.733	4.99		<.01	<.01
		.7	-.044	[-.292, .205]	.7319		.732	5.58		<.01	.01

Note. ^p<.1, *p<.05, **p<.01, ***p<.001. NA = Not Applicable (only for groups from the same measure); I^2 – total heterogeneity / total variability; τ^2 – estimated amount of total heterogeneity; $\sigma^2{}_1$ – Variance component of the 3-level model for the between-studies heterogeneity; $\sigma^2{}_2$ – Variance component of the 3-level model for the within-studies heterogeneity; RVE = Robust Variance Estimation; WM = Working Memory. This table represents the sensitivity analysis performed with three different correlational values (r = 0.3, 0.5, 0.7) since correlations between pre and posttest scores and between-studies were not reported in the original studies. r is the pre-posttest correlation and ρ is the between-study correlation. Results are consistent between the different correlations.

Table D

Sensitive Analysis for Control Groups

		Estimate	95% CI	*p*-value
POSTTEST	**Reasoning**			
	Merged	0.10	[-0.03,0.23]	.118
	Active control	0.14	[-0.04, 0.33]	.147
	Passive control	0.08	[-0.11,0.27]	.418
	Verbal WM			
	Merged	0.23	[0.07,0.39]	.006 **
	Active control	0.25	[0.03, 0.48]	.030 *
	Passive control	0.22	[0.005,0.43]	.045 *
	Visuospatial WM			
	Merged	0.23	[0.03, 0.43]	.025 *
	Active control	0.12	[-0.08, 0.31]	.234
	Passive control	NA	NA	NA
	Verbal STM			
	Merged	0.16	[-0.05,0.36]	.126
	Active control	0.16	[-0.09, 0.41]	.212
	Passive control	0.18	[-0.21,0.58]	.358
	Visuospatial STM			
	Merged	-0.03	[-0.39, 0.32]	.862
	Active control	0.03	[-0.27, 0.35]	.803
	Passive control	NA	NA	NA
FOLLOW-UP	**Reasoning**			
	Merged	0.13	[-0.09, 0.35]	.236
	Active control	0.13	[-0.14, 0.39]	.341
	Passive control	NA	NA	NA
	Verbal WM			
	Merged	0.23	[0.01, 0.46]	.045 *
	Active control	0.30	[-0.01, 0.60]	.055 ^
	Passive control	0.06	[-0.34, 0.46]	.756
	Visuospatial WM			
	Merged	0.14	[-0.09, 0.37]	.231
	Active control	0.14	[-0.11, 0.38]	.287
	Passive control	NA	NA	NA
	Visuospatial STM			
	Merged	0.18	[-0.10, 0.45]	.205
	Active control	0.28	[-0.05, 0.62]	.099 ^
	Passive control	NA	NA	NA
	Visuospatial STM			
	Merged	-0.04	[-0.33, 0.25]	.763.934
	Active control	-0.01	[-0.34, 0.31]	NA
	Passive control	NA	NA	

Note. ^p <.1, *p <.05, **p <.01. NA – Not applicable (analyses were performed only for constructs with more than 4 studies). Estimates, CI and P-values would not differ substantially if only studies with active control were included, except for Visuospatial WM in immediate posttest.

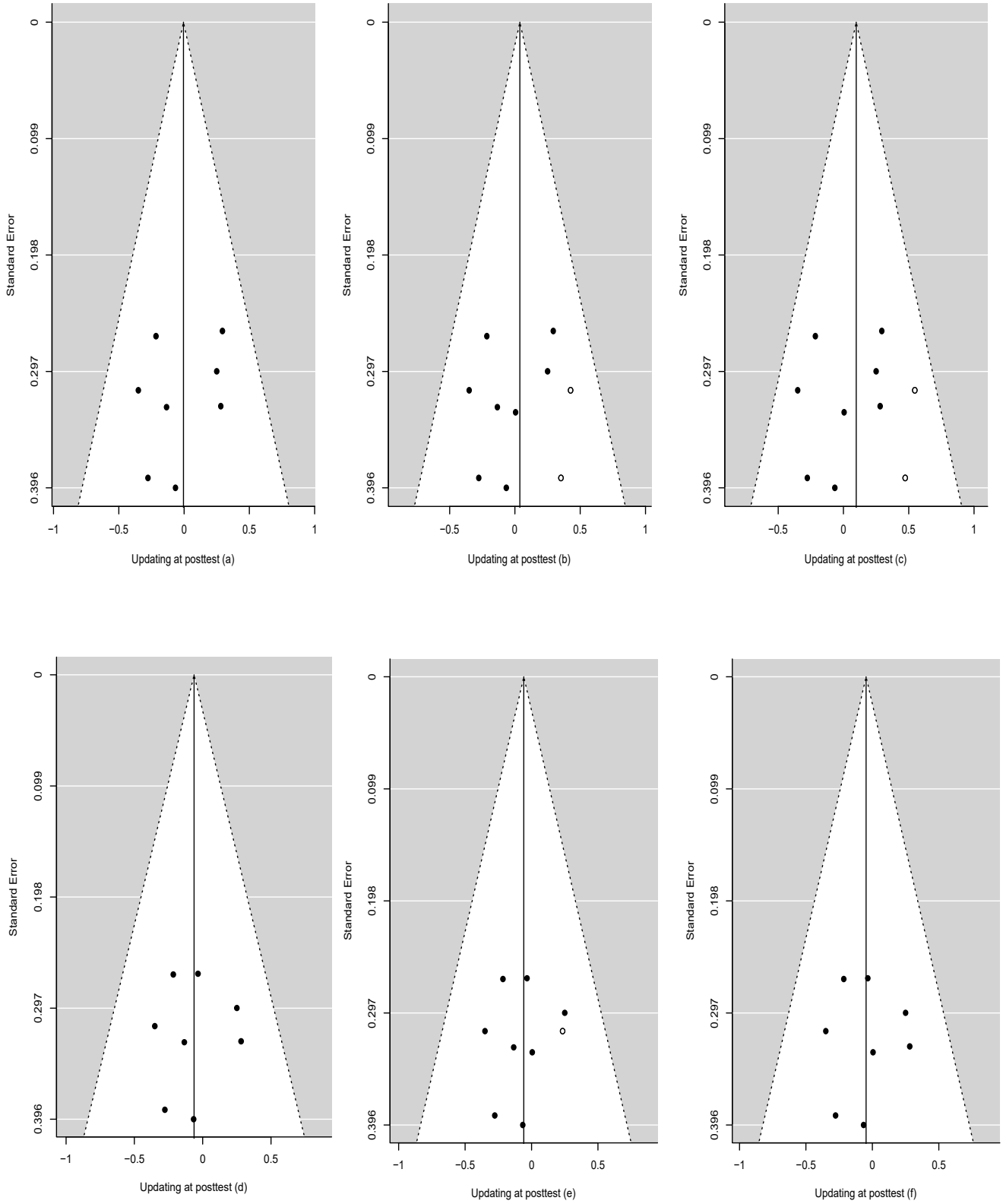

Figure A. Trim-and-fill Plots by Group (measure). Verbal WM – Updating. *Note.* For groups having at least two outcomes from the same trial, all possible combinations of subgroups, including exactly one outcome per trial, were considered to assess publication bias and the "leave-one-out" method.

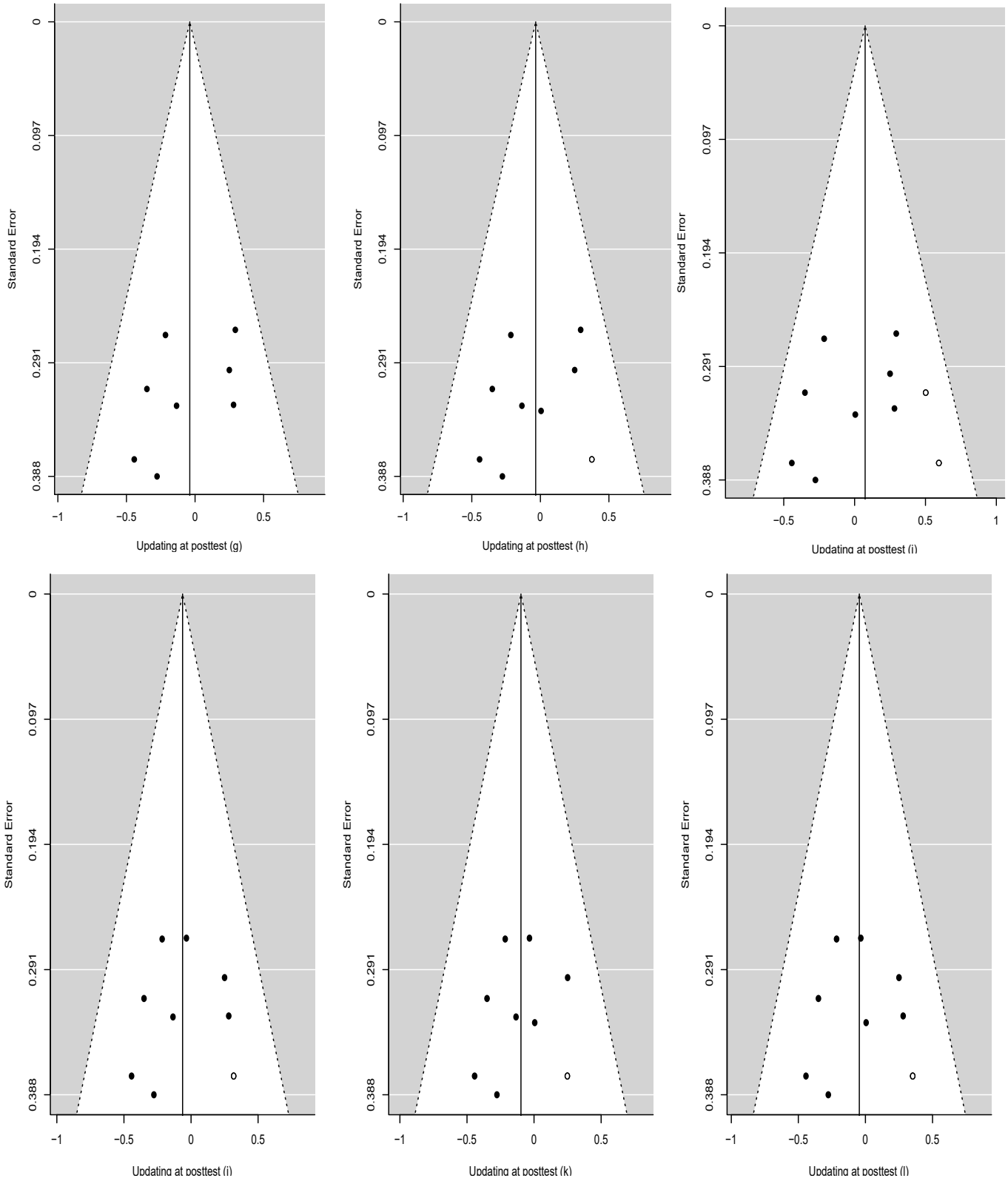

Figure A. (cont.). Verbal WM – Updating

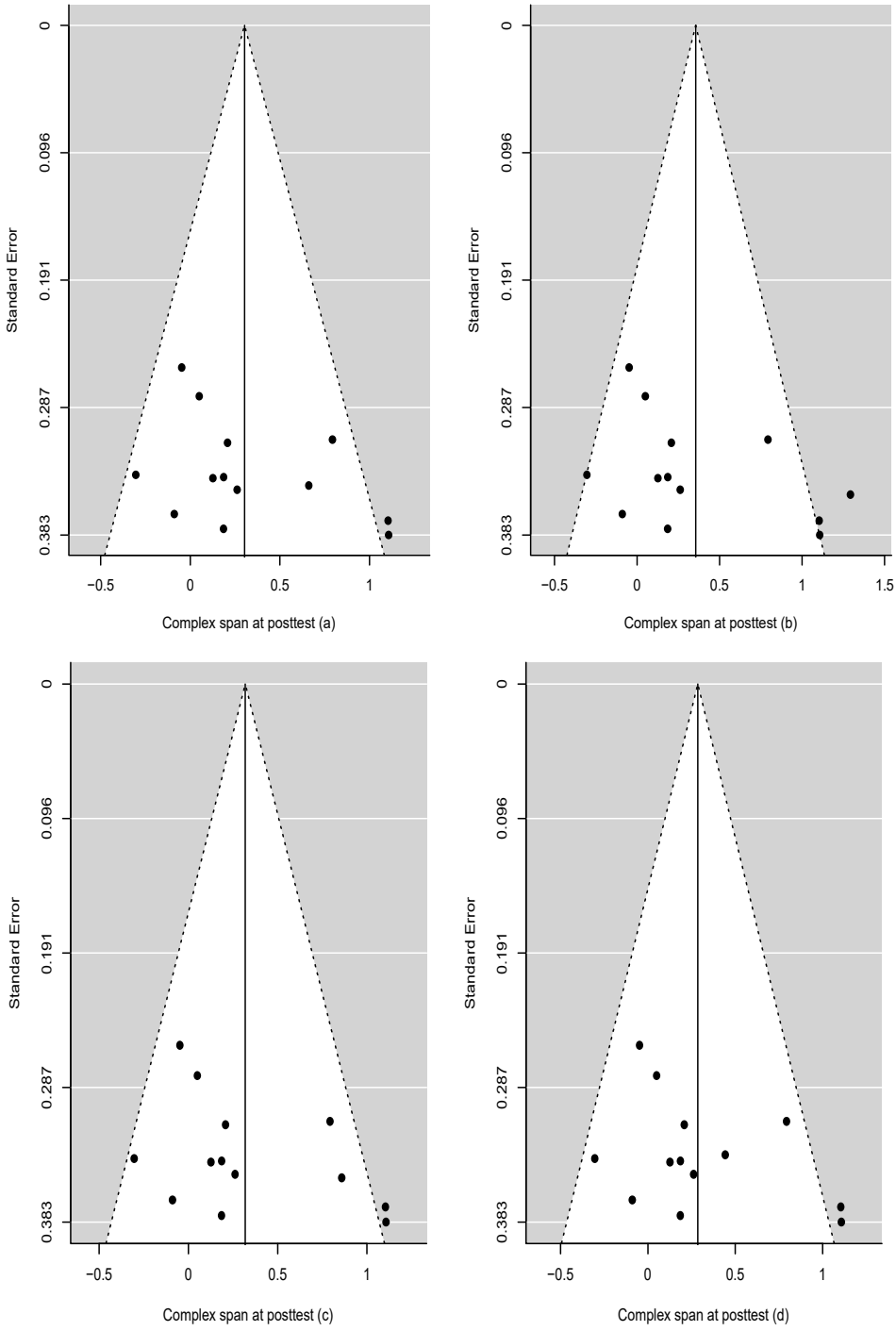

Figure A. (cont.). Verbal WM – complex span

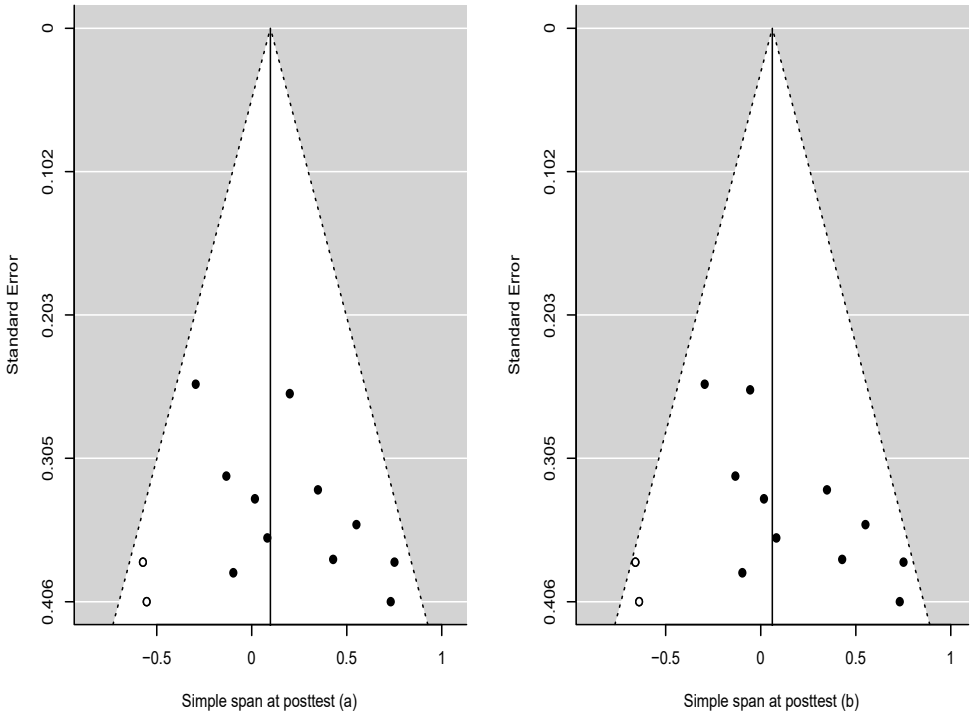

Figure A. (cont.). Verbal WM – STM

CHAPTER III

EFFECTS OF tDCS ON WORKING MEMORY IN HEALTHY OLDER ADULTS

Effects of transcranial direct current stimulation on working memory in healthy older adults: a systematic review[4]

Abstract

This mini systematic review aimed to investigate the effects of transcranial direct current stimulation (tDCS) on working memory in older adults without cognitive impairment. The search was carried out in three different databases for all human trials published from 2005 to 2015, assessing the effects of tDCS on working memory in healthy older adults. The screening was conducted by two independent reviewers. Four studies were included. All studies combined anodal tDCS (applied to pre-frontal or parietal cortex) with working memory training. Anodal tDCS seems to be able to modulate working memory performance. Nonetheless, there is evidence that suggests that variables, such as level of education, working memory task and time of assessment can moderate the effect. Recommendations for futures studies are also provided.

Keywords: working memory; older adults; transcranial direct current stimulation; tDCS.

[4] Teixeira-Santos, A. C., Nafee, T., Sampaio, A., Leite, J., & Carvalho, S. (2015). Effects of transcranial direct current stimulation on working memory in healthy older adults: a systematic review. *Principles and Practice of Clinical Research, 1*(3), 73-81.

Introduction

Aging is associated with structural and functional loss, affecting a wide range of cognitive skills, such as memory, language and executive function (Salthouse, 1996). These changes can have a negative impact on activities of daily living and quality of life and may result in disorders such as depression, mild cognitive impairment and dementia (e.g.: Alzheimer's disease and fronto-temporal dementia), ultimately becoming a significant burden on health-care systems (Christensen, Doblhammer, Rau, & Vaupel, 2009). Hence, growing interest emerges in an attempt to promote healthy aging, optimizing cognitive skills and remediating cognitive impairment.

Among the cognitive skills affected by the aging process, working memory (WM) stands out due its notable decline throughout the individual's lifespan. The decline begins in the mid-20s and concerns both visuospatial and verbal aspects of WM (Park et al., 2002). WM is a mental workspace in which information is maintained and processed over a short period of time while a task is being performed (Baddeley, 2003). WM is related to several higher order cognitive functions such as reading (Daneman & Carpenter, 1980), mathematics (Gathercole, Pickering, Knight, & Stegman, 2003), intelligence (Conway, Kane, & Engle, 2003; Kyllonen & Raymond, 1990; Miyake, Friedman, Rettinger, Shah, & Hegarty, 2001), prospective memory (Braver, Paxton, Locke, & Barch, 2009), processing speed (Fry & Hale, 2000), attention (Engle & Kane, 2004), perceptual organization (Woodman, Vecera, & Luck, 2003) and general language (Kemper, Herman, & Liu, 2004).

The mechanisms underlying WM decline are unclear. Normal Functional brain alterations have been reported in healthy older adults; greater bilateral activation has been found in healthy older adults during a WM task compared to younger adults. This phenomenon is thought to represent a functional reorganization and compensation mechanism by the recruitment of additional resources in order to maintain cognitive performance (Rajah & D'Espósito, 2005; Schulze et al., 2011). Also normal aging is followed by structural loss in brain tissue (Ge et al., 2002; Good et al., 2001; Raz, Rodrigue, & Haacke, 2007), mainly in prefrontal brain regions (Raz & Rodrigue, 2006). Given the centrality of WM in these higher order cognitive functions and its substantial decline over aging, new strategies to reduce the impact of WM loss in this population are sorely necessary.

In the past few years, there has been a growing interest in non-invasive brain stimulation techniques and the development of new combined interventions that can be used as rehabilitation strategies. Transcranial direct current stimulation (tDCS) is one such NIBS. Given the safety profile, high

tolerability, affordable cost, and few side effects, tDCS has been widely used in both healthy and clinical populations (Gandiga, Hummel, & Cohen, 2006; Solé-Padullés et al., 2006). The most common side effects associated with tDCS are itching, tingling, headache, burning sensation and discomfort (Brunoni et al., 2011). tDCS has already been shown to improve performance in several cognitive domains such as perception, attention, working memory, learning and decision making (Shin, Foerster, & Nitsche, 2015). tDCS changes cortical activity through weak electric currents, producing changes in membrane resting potential and hence in brain activity (Fregni & Pascual-Leone, 2007; Nietsche et al., 2008; Paulus, 2011). In tDCS a weak current (1-2mA) is delivered through the scalp, for a duration of up to 30 minutes. tDCS modulates membrane excitability of neurons in the regions underlying the electrodes (Purpura & McMurtry, 1965; Scholfield, 1990). The direction of this modulatory effect depends on the stimulation polarity; anodal stimulation increases excitability, while cathodal stimulation decreases it (Nitsche & Paulus, 2000). It is also notable that depending on the intensity, duration and research protocol, non-linear effects have also been reported (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013).

There is evidence to suggest that the application of tDCS on the prefrontal cortex (PFC) (Andrews, Hoy, Enticott, Daskalakis, & Fitzgerald, 2006; Boggio et al., 2006; Fregni et al., 2005; Jo et al., 2009; Zaehle, Sandmann, Thorne, Jäncke, & Herrmann, 2011), posterior PC (parietal cortex) (Sandrini, Fertonani, Cohen, & Miniussi, 2012) and cerebellum (Ferrucci et al., 2008) may modulate WM. Specifically in older populations, there are several studies that report noninvasive brain stimulation such as tDCS can have positive effects on cognitive function in typical and pathological aging (Hsu, Ku, Zanto, & Gazzaley, 2008). Therefore, the aim of this review paper is to summarize the current literature on the effects of tDCS on WM performance improvement in healthy older adults.

Methods

We conducted database searches using PubMed, Web of Science, and Science Direct to identify human trials, written in English, from 2005 to 2015. The search terms used were “transcranial direct current stimulation”, “tDCS”, “aging”, “elderly”, “older adults” and “working memory” (details about the search strategy can be found in Appendix A). Two authors independently examined the titles and

abstracts in order to exclude articles that did not meet inclusion criteria. Subsequently, the two reviewers examined the full text independently in order to identify relevant papers.

The inclusion criteria for the review were (1) *population:* studies had to include at least one group of healthy participants aged over 55 years old; (2) *intervention:* tDCS, regardless of the number of sessions and if the stimulation is or is not associated with cognitive training; (3) *assessment instrument* – studies had to assess working memory both before and after intervention; (4) *study design:* studies had to be sham controlled trials published in a peer reviewed journal.

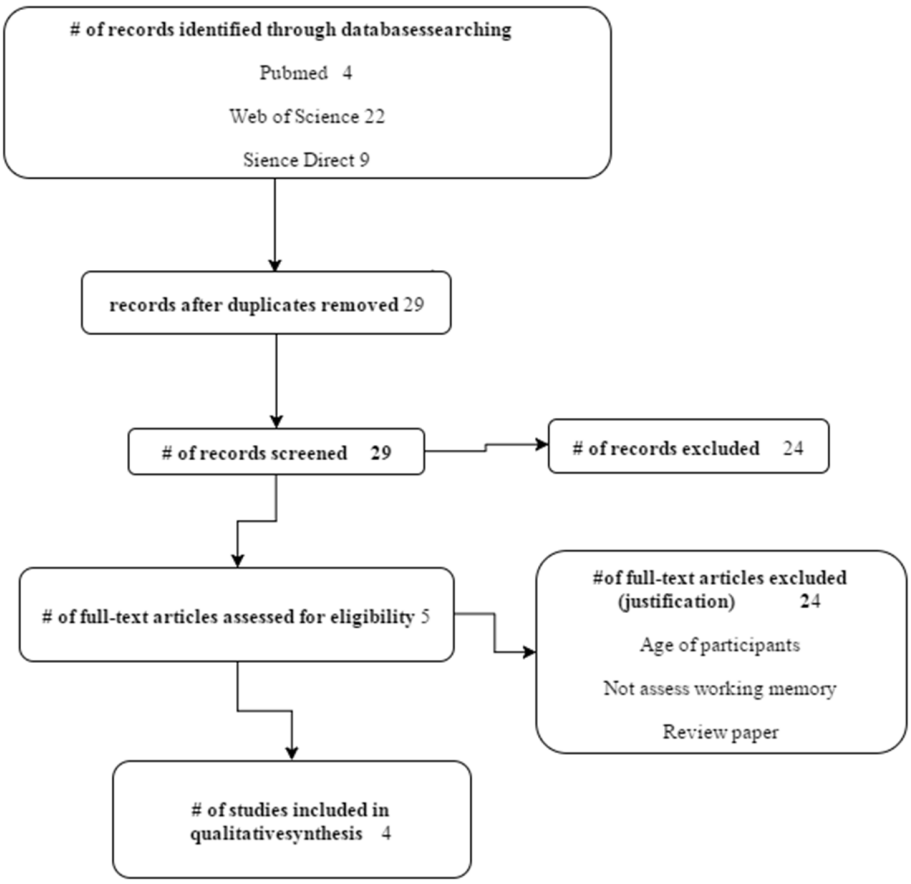

Figure 1. Flowchart for identifying eligible studies.

Results

Included studies

The results of the screening carried out by the two independent authors were exactly the same, with no disagreements. A total of 29 papers were found in the search after eliminating duplications across search engines. Twenty-four articles were excluded in the initial screening due to age of participants, assessment (some of the studies did not assess working memory) and study design (some of them were literature review papers). We reviewed the full text of the remaining five articles and one of the papers was excluded due to low age of participants. Finally, four articles were included in the systematic review.

Table 1 summarizes the characteristics of the studies. In terms of the methodological quality of the included studies, random allocation was explicitly described for three trials (Berryhill & Jones, 2012; Jones, Stephens, Alam, Bikson, & Berryhill, 2015; Park, Seo, Kim, & Ko, 2014). There was one paper that did not describe the randomization method or how participants were allocated to the experimental/placebo group (Seo, Park, Seo, Kim, & Ko, 2011). Two studies were single-blind designs (Berryhill & Jones, 2012; Jones et al., 2015) and two were double-blind designs (Park et al., 2014; Seo et al., 2011). All studies used a sham-controlled design and carried out a screening phase using the Mini-Mental State Examination (MMSE) to ensure that participants were cognitively healthy older adults. In three of the studies participants were right handed subjects (Berryhill & Jones, 2012; Jones et al., 2015; Seo et al., 2011) while in one of the studies handedness was not reported (Park et al., 2014).

Intervention

Only two studies applied repeated sessions of tDCS (Jones et al., 2015; Park et al., 2014). In both of them tDCS was administered during 10 days. One study had a multiple outcome design; evaluating sham stimulation versus anodal tDCS to the left (F3) or right (F4) PFC in an intra-subject analysis and also the effect of educational level in a between-subject analysis (Berryhill & Jones, 2012). One study had a single session of tDCS (Seo et al., 2011). The duration of stimulation in two studies was 10 minutes (Berryhill & Jones, 2012; Jones et al., 2015) and 30 minutes in the other two (Park et al., 2014; Seo et al., 2011). Two studies used a current density of 0.043 mA/cm2 (Berryhill & Jones,

2012; Jones et al., 2015), while the other two used a 0.08 mA/cm2 current density (Park et al., 2014; Seo et al., 2011).

Furthermore, all studies combined cognitive training with tDCS. Two studies delivered stimulation while participants were engaged in a cognitive task (Park et al., 2014; Seo et al., 2011) while the other two studies used an "offline" design, in which participants performed the task after receiving tDCS (Berryhill & Jones, 2012; Jones et al., 2015). However, in the two offline studies, participants performed practice trials while receiving stimulation. Additional add-on training was not reported in any of these papers.

The cognitive training tasks targeted both verbal and visuospatial subcomponents of working memory: verbal 2-back (Berryhill & Jones, 2012; Seo et al., 2011); visual 2-back (Berryhill & Jones, 2012; Jones et al., 2015); visuospatial WM task (Jones et al., 2015; Seo et al., 2011) and Ospan (Jones et al., 2015). Park and colleagues (2014) used the Korean computer-assisted cognitive training (CACT) Program (Glisky, Schacter, & Tulving, 1986) although they did not provide details about the specific tasks composing the program. In all trials the difficulty level of the task was not adaptive.

In regards to treatment protocol, the electrode size used in most of the studies was 5x7cm, with the exception of Seo et al. (2011) who used 5x5cm electrodes. All the studies used anodal stimulation, targeting the left or right dorsolateral prefrontal cortex (DLPFC) (F3, F4) or right PC (P4). In all studies, reference electrodes were placed in an extra-cephalic region (cheek or arm). One study presented a follow-up assessment 1 month after training (Jones et al., 2015) while Park et al. (2014) performed a follow-up after 7 and 28 days.

Table 1

Characteristics of the Studies Included in the Review

Author (year)	Type of study	Sample size	Age (in years)	current density (mA/cm2)	Offline/ online task	# of arms	Anodal electrode[5]	Cathodal electrode	Size (active/ return in cm2)	Task	number of sessions / duration	Follow-up	Primary outcomes	Secondary outcomes	Main results
Berryhill & Jones (2012)	Rand Placebo Single-Blind	N=25 Did not mention gender	56-80	.043	Offline (however participants performed practice trials online)	Cross-sectional	F4 F3	contralateral cheek	35/35	Verbal/ visual 2-back	3 (1 session for each condition : F3/F4/ sham) 10 min	No	Verbal/ visual 2-back	n/a	- No significant effect before divide the group in two samples according to the level of education. - tDCS was uniformly beneficial across sites and WM tasks in older adults with more education. - In the low education group, tDCS impaired visual WM performance and had no effect on verbal WM.
Jones et al. (2015)	Rand. Placebo Single - Blind	N=72 (18 in each arm) 49 females	55-73	.043	offline (however participants performed practice trials online)	4 *Sham* *PFC* *PC* *PC/PFC*	F4 P4 F4/P4	contralateral cheek	35/35	Visuospatial working memory and OSpan task	10/10 min	Yes 1 month	Visuospatial WM task and Ospan	Stroop, digit span and spatial 2-back	-The current flow to identify the spatial extent of brain stimulation were modeled. tDCS to the PFC supplied current to PFC regions and also to orbitofrontal and ventral temporal regions. The PC stimulation target PC and posterior occipital and ventral temporal regions. There was considerable overlap of current flow in both areas - All groups showed equivalent improvement immediately after 10 sessions of training. However only the active tDCS group maintained significant improvements at follow-up. -All active tDCS groups resulted in equivalent benefits. -The more challenging and adaptive task (recall and Ospan tasks) showed great gains compared to recognition tasks. - The largest transfer effect was observed in the most difficulty near

Table 1 (Cont.)

														transfer task, the spatial 2-back. The two other near transfer measures, the Stroop task and the digit span showed no transfer effects.
Park et al. (2014)	Rand. Placebo Double-Blind	40 (20 sham/ 20 active) 27 females	>=65	.08	online	2 *Anodal bilateral (F3/F4) Sham*	F3 and F4 (bilateral)	Nondominant arm	25/25	CACT program	10 30 min	Yes (7 and 28 days)	Accuracy and response time in a verbal 2-back task and digit span forward.	Verbal learning test, visual span test, CPT, word–color test, trail making test	-Accuracy of the verbal WM task increased significantly for up to 28 days. -The reaction time of the verbal WM task was significantly shortened in the real stimulation group only in the last day of stimulation. -Improvement in digit span forward in the active group observed only 7 days after stimulation. - No improvement in the other transfer measures
Seo et al. (2011)	No information about rand. Placebo Double-Blind	24 (12 sham/ 12 active) 10 females	65-78	.08	online	2 *F3 sham*	F3	Left arm	25/25	Verbal 2-back and visuospatial WM task	1 30 min	No	Accuracy and response time on a verbal 2-back and visuospatial WM task	n/a	- Improvement of the verbal WM performance observed in the active group - For reaction time, there was not a significant effect of tDCS. -No difference in visuospatial working memory performance.

Notes: Rand = Randomized; n/a = not applicable. Electrode positions refer to the International 10 20 EEG system (Jasper, 1958)

Outcome measures

Several outcome measures were used in the selected studies: verbal 2 back (Berryhill & Jones, 2012; Park et al., 2014; Seo et al., 2011), visual 2-back (Berryhill & Jones, 2012; Jones et al., 2015), visuospatial WM task (Jones et al., 2015; Seo et al., 2011), Ospan (Jones et al., 2015), Stroop (Jones et al., 2015), digit span forward (Jones et al., 2015; Park et al., 2014), digit span backward (Park et al., 2014), verbal learning test (Park et al., 2014), visual span test (Park et al., 2014), Continuous Performance Task (CPT) (Park et al., 2014), word-color test (Park et al., 2014) and trail making test (Park et al., 2014).

In general, the literature indicated that tDCS had a positive effect on working memory by improving verbal and visual working memory performance. Interestingly, Berryhill and Jones (2012) did not find significant effect of anodal tDCS on WM, when comparing to sham, immediately after stimulation. However, subgroup analysis demonstrated that older adults with higher levels of education had significant improvement in working memory performance after stimulation, having no difference between the stimulation in F4 and F3 or between verbal and visual tasks. In the group of lower educational levels, the stimulation had negative effects on visual WM performance and had no effects on verbal WM. Jones et al. (2015) modulated the current flow to identify the spatial extent of brain stimulation after anodal tDCS to the PFC and PC and they found that tDCS to the PFC supplied current to PFC regions and also to orbitofrontal and ventro-temporal regions. The PC stimulation targeted PC and posterior occipital and ventral temporal regions. There was considerable overlap of current flow in both areas. They have also identified that both active and control tDCS groups (PFC, posterior parietal cortex - PPC, PFC/PPC and sham) showed equivalent improvement immediately after 10 sessions of training. However only the active tDCS group maintained significant improvements at the 1-month follow-up for both trained and non-trained tasks. All active tDCS groups (PFC, PC, PFC altering with PC) resulted in equivalent improvements. Jones and colleagues also reported that the more challenging and adaptive tasks (recall and Ospan tasks) showed greater improvements when compared to recognition tasks. The largest transfer effect was observed in the most difficult near transfer task, the spatial 2-back. The two other near transfer measures, the Stroop task and the digit span showed no transfer effects. Park et al. (2014) showed that improved verbal WM accuracy was sustained for up to 28 days, after 10 sessions of computer-based cognitive training combined with bilateral anodal tDCS of the PFC (F3 and F4). The

reaction time of the verbal WM task was significantly shortened in the real stimulation group only in the last day of stimulation and not in the follow up. They also reported a near transfer effect, namely improvement in digit span forward in the active group that was observed only 7 days after stimulation. Finally, Seo et al. (2011) failed to find differences in visual working memory performance following tDCS, but they reported verbal WM improvements in the active group. There was no significant effect of tDCS in reaction time in both visuospatial and verbal working memory performance.

Adverse effects

Two studies reported the following adverse effects: minimal skin discoloration on the arms for a few days (Park et al., 2014) and transient aching and redness on the arm (Seo et al., 2011).

Variables mediating the tDCS effect

Berryhill and Jones (2012) demonstrated that the educational level has been a potential effect modifier, with participants with higher levels of education benefiting more from the intervention. Modality of working memory (verbal or visual) can also be influenced differently by tDCS. Seo et al. (2011) found positive effect of intervention only on verbal WM performance of the active group, having no difference in visuospatial WM performance. Berryhill and colleagues (2012) reported impairment in visual working memory of lower educational group. Time of assessment can also mediate the effects. Jones et al. (2015) reported that both active (PFC,PPC, PFC/PPC) and sham tDCS groups showed equivalent improvement immediately after 10 session of training. However only the active tDCS group maintained significant improvements on trained and non-trained tasks at follow-up a month later.

Discussion

The aim of this paper was to review the literature on tDCS effects on the WM performance of healthy elderly people. We found four papers that met our criteria. Most of the studies were randomized and included sham controlled blinded trials. The included studies showed that WM training administered with anodal tDCS over the PFC and PC can enhance WM, and these positive effects can be transferred to tasks similar to those used in the WM training.

In the elderly, the effects of tDCS on WM seem to have a similar pattern to the one showed with young adults, in which anodal tDCS over the left DLPFC improves WM (Richmond, Wolk, Chein, & Olson,

2014). However, this enhancement was found only in the verbal component of working memory, as was the case in Seo et al. (2011). Indeed, Berryhill and colleagues (2012) reported an impairment in visual WM performance after stimulation in older people with lower educational level, which was more evident during stimulation of the right PFC (F4). Richmond et al. (2014) argue that this absence of results and negative effects of tDCS on visuospatial WM could be due to stimulation of the left hemisphere, since the left side is associated with verbal contents and the right side is responsible for visuospatial processing (Reuter-Lorenz et al., 2000).

The WM task used in training can be adaptive; the difficulty level adapts to match the participant ability, and it can be increased throughout training according to the improvement of the participant's proficiency. All the studies in this review adopted a non-adaptive WM task; the task had the same level of difficulty for all participants and was not adjusted according to the performance of the subject. One meta-analysis of WM training in an elderly population (Karbach & Verhaeghen, 2014) failed to recognize a difference between adaptive and non-adaptive training paradigms, which suggests that utilizing an adaptive structure of WM training not improve the quality of WMT.

Finally, a neuroimaging study showed that a single session of anodal tDCS administered to the left inferior frontal gyrus can temporarily reverse changes in brain activity and connectivity in older adults (Meinzer, Lindenberg, Antonenko, Flaisch, & Flöel, 2013). In that study, a decrease in bilateral hyperactivity related to the intervention was observed, suggesting a "youth-like" connectivity pattern during resting state fMRI (Meinzer et al., 2013).

In one of the studies (Berryhill & Jones, 2012), tDCS was beneficial in older adults if they had a higher level of education. However, in the study by Berryhill and Jones (2012), the group with relatively lower education was in school for an average 13.5 years (comparing to 16.9 on the higher level of education). These effects may be due to differences on cognitive reserve. Thus, older adults with higher educational level may present differences in the flexibility and adaptation of cognitive networks (Stern, 2013). It would be interesting to further examine the effect of educational level within groups with lower educational level or even with illiterate participants. Additionally, it is important to verify if other variables such as genetic factors, gender, age and personality can mediate the intervention effect.

Half of the studies included in this review had an online cognitive training (Park et al., 2014; Seo et al., 2011), which means that the training was performed simultaneously with application of tDCS. The other half of the studies used an offline design, meaning that the task was carried out after

stimulation (Berryhill & Jones, 2012; Jones et al., 2015). However, in the two offline studies, participants performed practice trials while receiving tDCS. Both kinds of stimulation (online and offline) showed similar results, which would be expected since the physiological effects of tDCS have been reported to last for more than one hour after several minutes of stimulation, and the participants of the offline studies performed the practice trial during stimulation (Nitsche & Paulus, 2000). Nevertheless, it is worth pointing out that there is evidence that online and offline tDCS can have differential effects. For instance, anodal tDCS over the motor cortex increases motor learning when applied during the task, while offline tDCS has the opposite effect (Stagg et al., 2011). Moreover, online anodal tDCS over the left DLPFC is more effective on skill acquisition following two days of WM training than offline tDCS (Martin, Liu, Alonzo, Green, & Loo, 2014). In line with this finding, a neuroimaging study reported greater brain activation during stimulation compared to the period following stimulation (Stagg et al., 2013). Further studies should explore the effects of tDCS timing during WM training in elderly people.

Repetitive sessions of tDCS are thought to boost the effects of stimulation, since single stimulation has relatively short after-effects (Nitsche et al., 2008; Nitsche & Paulus, 2000). The main assumption underlying the effects of repetitive sessions is that it will change the mechanisms of synaptic plasticity, such as long-term potentiation and long term depression (Fritsch et al., 2010; Nitsche, Fricke, et al., 2003; Nitsche et al., 2004; Nitsche, Schauenburg, et al., 2003; Rroji, van Kuyck, Nuttin, & Wenderoth, 2015). Long-term potentiation is activity-dependent plasticity that induces an increase of synaptic transmission, while long-term depression reduces the efficacy of synaptic transmission (Bliss & Cooke, 2011). Therefore, the use of repetitive sessions of tDCS may induce learning in the neural networks which will ultimately benefit cognitive training (Brunoni et al., 2013). Among the papers analyzed, we identified only two studies showing the effect of repeated tDCS sessions on WM in older people (Jones et al., 2015; Park et al., 2014) which is in line with findings reported with younger people (Baker, Rorden, & Fridriksson, 2010; Glisky et al., 1986; Hamilton, Chrysikou, & Coslett, 2011; Iuculano & Kadosh, 2013; Kim, Han, Ahn, Kim, & Kim, 2012; Loo et al., 2012; Martin et al., 2013; Reis et al., 2009). In both studies (Jones et al., 2015; Park et al., 2014) participants received intervention five days a week for 2 weeks. There is no concrete evidence of the optimal sessions frequency and duration of tDCS, however the cumulative effects of motor cortical excitability in daily sessions of anodal tDCS seem to be greater compared to sessions separated by a two day interval (Alonzo, Brassil, Taylor, Martin, & Loo, 2012). Similar results were found in stroke patients in which the cumulative effects of motor function

was associated with five daily sessions, but not associated with weekly sessions of tDCS (Boggio et al., 2007). Additionally, tDCS has been reported to have different effects depending on the duration of stimulation. Three minutes have been reported as the minimum required time to induce an after-effect; and longer periods (i.e. more than 30-min) have produced mixed results (Batsikadze et al., 2013; Monte-Silva et al., 2013). There is also the possibility that the baseline level of cortical activity in a given neural network can modify subsequent modification to that network (Carvalho et al., 2015). Although it is costlier and logistically difficult to carry out studies with multiple sessions compared to single sessions, investment in this area is warranted and may significantly contribute to development of this field. This would go a long way to validate the effectiveness of this type of intervention, as well as standardize the tDCS intervention protocol in terms of the number of sessions, interval between sessions and duration of stimulation.

The optimized site of tDCS is another issue that needs consideration. Based on computer modeling, the largest effects induced by tDCS polarity are elicited beneath the stimulation electrode (Wagner et al., 2007). However, tDCS over different stimulation locations (such as bi-hemispheric, unihemispheric, prefrontal, parietal, prefrontal alternating with parietal and right and left) can lead to similar effects on WM. It is important to have active stimulation targeting an area that is not related to WM in order to determine whether similar effects can be observed by stimulating any given area of brain (Jones et al., 2015). Moreover, as most of tDCS effects so far have been on the verbal subcomponent of WM, it will be important to test different targets in order to increase other subcomponents, such as the visual.

Finally, our results provide evidence of the safety of tDCS in elderly people, as only minor adverse effects were reported among studies.

Conclusion

In sum, anodal tDCS over the PC and PFC seems to improve WM in healthy elderly subjects, and those improvements can be sustained up to one-month post-intervention. However, better parameters of stimulation are still required before mainstream use.

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Appendix B

Supplementary material (study II)

PUBMED

("transcranial direct current stimulation"[Title/Abstract] OR "tdcs"[Title/Abstract]) AND ("aging"[Title/Abstract] OR "elderly"[Title/Abstract] OR "old* adult*"[Title/Abstract]) AND "working memory"[Title/Abstract]

Results: 3

WEB OF SCIENCE

Search for TOPIC (title, abstract, author keywords, keywords plus) All databases

Tópico: ("transcranial direct current stimulation"[) OR Tópico: (tdcs) AND Tópico: ("working memory") AND Tópico: ("Aging") OR Tópico: (old* adult*) OR Tópico: ("elderly")

Restults: 22

SCIENCE DIRECT

tak("Transcranial Direct Current Stimulation") OR tak("tdcs") AND tak("Working memory") AND tak("Aging") OR tak("old* adult*") OR tak("elderly").

All years

Results: 9

Data of search: October 5, 2015.

CHAPTER IV

TRANSFER EFFECTS OF WORKING MEMORY TRAINING COUPLED WITH tDCS IN OLDER ADULTS

Cognitive transfer effects of working memory training coupled with transcranial direct current stimulation in healthy older adults: a double-blinded, randomized, sham controlled experiment[6]

Abstract

Background: Working memory training (WMT) has been used for cognitive enhancement in older adults. Furthermore, transcranial direct current stimulation (tDCS) has been used to boost the effects of WMT. Nevertheless, there is limited evidence on the combination of tDCS and WMT efficacy in older people.

Objective: The present study aimed to assess the immediate effects of tDCS coupled with WMT and, whether those effects are maintained at a 15-day follow-up in 54 healthy older. We also explored if baseline performance, age and educational level modified the effects of treatment.

Method: In this double-blind randomized placebo-controlled experiment, participants were randomized into three groups: anodal-tDCS+WMT; sham-tDCS+WMT or double-sham. Five-sessions of tDCS (2mA) were applied over the left dorsolateral prefrontal cortex (DLPFC). Near transfer effect was assessed through Digit Span and Corsi Block-tapping Test, while far transfer was measured by Raven Advanced Progressive Matrices (RAPM) and Digit-symbol Coding.

Results: Multilevel modeling analysis showed that only the group with anodal-tDCS+WMT displayed a significant improvement from pretest to follow-up in measures of reasoning (RAPM) and short-term memory (forward digit span). Near transfer gains predicted gains in far transfer. Moreover, there was no

[6] Publications derived from this study:

Peer reviewed publications in print or other media

Teixeira-Santos, et al. (2019). Can tDCS enhance transfer effects of working memory training in older adults? Manuscript in preparation.

Abstracts, Poster Presentations and Exhibits Presented at Professional Meetings

Teixeira-Santos, A.C, Moreira C.S., Pereira, D.R., Carvalho S., Sampaio A. (2019). Transfer effects of anodal transcranial direct current stimulation coupled with working memory training in healthy older adults: a randomized controlled trial. Poster session accepted at the International Conference AGENortC, Viana do Castel, Portugal.

Teixeira-Santos, A.C., Pereira, D.R., Alves, S., Leite, J., Carvalho, S., & Sampaio, A. (2018) Can tDCS enhance transfer effects of working memory training in older adults? Poster session presented at the 4º Congresso da Ordem dos Psicólogos Portugueses, Braga, Portugal.

Teixeira-Santos, A.C., Pereira, D.R., Alves, S., Leite, J., Carvalho, S., & Sampaio, A. (2018). Can tDCS enhance transfer effects of working memory training in older adults? Abstract available at Abstracts of ongoing projects supported by the Bial Foundation (www.fundacaobial.com).

strong evidence that supported age, educational level, baseline performance, and general cognitive ability as predictors of reasoning gains.

Conclusion: WMT coupled with anodal-tDCS may improve short-term memory and reasoning in older adults, with the effects most strongly observed at follow-up.

Keywords: working memory training; aging; tDCS; neuroplasticity; individual differences.

Introduction

Working memory (WM), a temporary set of mental components in which information is held and available for ongoing information processing (Cowan, 2017), is a core process for many higher-order cognitive functions (Glisky, 2007). It is among the most impaired cognitive functions in elderly people (Kirova, Bays, & Lagalwar, 2015; Murman, 2015). Considering that 13% of world population is aged 60 or more and that the prevalence of mild cognitive impairment within this stage ranges from 3% to 42%, it is of paramount importance to develop strategies to preserve cognitive functioning in this population (United Nations, Department of Economic and Social Affairs, & Population Divison, 2017; Ward, Arrighi, Michels, & Cedarbaum, 2012). Therefore, working memory training (WMT) has been proposed as a prominent intervention in the elderly, which may benefit not only WM, but also other cognitive processes related to it. However, the results of different studies are controversial (Karbach & Verhaeghen, 2014; Melby-Lervåg & Hulme, 2013, 2016; Melby-Lervåg, Redick, & Hulme, 2016). In this sense, other techniques have been developed to promote cognitive enhancement in the elderly (Davis, 2017; Strenziok et al., 2014). Among them, transcranial direct current stimulation (tDCS) has been tested as an add-on tool to boost WMT (Teixeira-Santos, Nafee, Sampaio, Leite, & Carvalho, 2015).

Most of the studies in which tDCS was used as add-on, have been conducted with younger adults, and report that anodal tDCS (atDCS) over the DLPFC may improve WM performance (Fregni et al., 2005; Ke et al., 2019; Ohn et al., 2008; Zaehle, Sandmann, Thorne, Jäncke, & Herrmann, 2011).

However, these studies were performed in a single tDCS session, and recent literature has suggested a beneficial effect of repeated sessions (Alonzo, Brassil, Taylor, Martin, & Loo, 2012; Gálvez, Alonzo, Martin, & Loo, 2013; Hsu, Ku, Zanto, & Gazzaley, 2015; Martin et al., 2013).

Few studies have combined WMT with tDCS in elderly people, showing improvements on the trained task, as well as, transfer effects, which were found even a month after training (Jones, Stephens, Alam, Bikson, & Berryhill, 2015; Park, Seo, Kim, & Ko, 2013). On the other hand, Nilsson et al. (2017) failed to find transfer effects in a 20-session tDCS coupled with an executive functioning protocol in older adults. The same team also performed a single session cross-over trial comparing 1mA with 2mA atDCS and a sham condition (stDCS) in older people and failed to find superiority of the stimulation conditions in a n-back task performance (Nilsson, Lebedev, & Lövdén, 2015). Additionally, individual differences (i.e., age, baseline cognitive performance, general cognitive ability and educational level) seem to

interact with WMT and tDCS (Berryhill & Jones, 2012; Borella, Carbone, Pastore, De Beni, & Carretti, 2017; Gözenman & Berryhill, 2016; Ke et al., 2019; Ruf, Fallgatter, & Plewnia, 2017).

Considering this mixed evidence regarding the effects of tDCS coupled with WMT in older adults, in this study, we assessed the effects of 5-day tDCS coupled with dual n-back training, after training and in a 15-day follow-up in healthy older adults.

In this experiment, the main outcomes were WM tasks (near transfer), as well as, a reasoning task (far transfer). We expected that both WMT groups will present near transfer when compared to the double-sham group. However, we believed that far transfer for reasoning would be verified only in atDCS+WMT group. Since far transfer has not been demonstrated in WMT alone (Salminen, Frensch, Strobach, & Schubert, 2016), we hypothesized that tDCS could boost training, improving its generalization. Additionally, we expected that near transfer gains would predict far transfer gains, since it is postulated that far transfer is due to plasticity in WM (Melby-Lervåg & Hulme, 2013). An additional analysis explored whether vocabulary, general cognitive ability, age, and educational level modulated WMT effects.

Methods

Study design

A CONSORT (Consolidated Standards of Reporting Trials) diagram is presented in Figure. Participants and assessors were blinded to both stimulation and task conditions. Stimulation sessions and assessments were performed by different researchers. The randomization list was generated in a website (http://www.randomization.com) in blocks of 6 with a ratio of 2:2:2. The allocation list was masked from all investigators. The condition of each participant was described in different excel sheets in a way that the researcher responsible for the randomization had access only to the allocation of the next participant (allocation concealment).

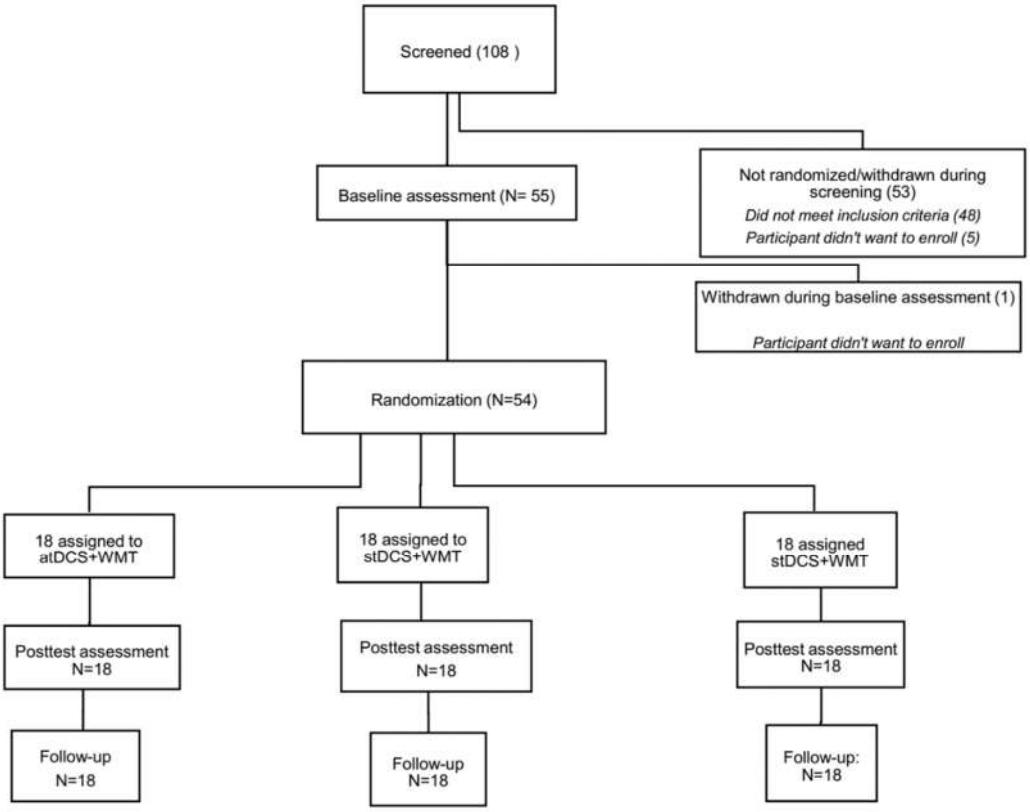

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram.

Participants

Fifty-four participants (68.20 ± 5.92 years old) were randomized to one of three groups: 1) atDCS+WMT; 2) stDCS+WMT; 3) double-sham. All participants were right-handed, with normal or corrected-to-normal visual (≥20/40 in both eyes) and auditory acuity, with no history of neurological/psychiatric disorders, substance abuse or recent use of psychotropic medication, nor contraindication for tDCS. Participants were recruited in senior daycare centers and in sport and recreation clubs. See Supplementary Table S1 for group differences at baseline. All included participants scored above MoCA cut off (of 2 standard deviation) for cognitive impairment following the normative score of the Portuguese population, considering age and education (Freitas et al., 2011). Participants scoring above 9 in GDS (Pocinho, Farate, Dias, Lee, & Yesavage, 2009) were excluded. The study was performed in accordance with the Declaration of Helsinki and approval was obtained from the ethics

subcommittee for life and health sciences of University of Minho (SECVS 012/2016). Participants gave informed consent before their inclusion in the study.

Procedure

Participants underwent 11 sessions as depicted in Figure.

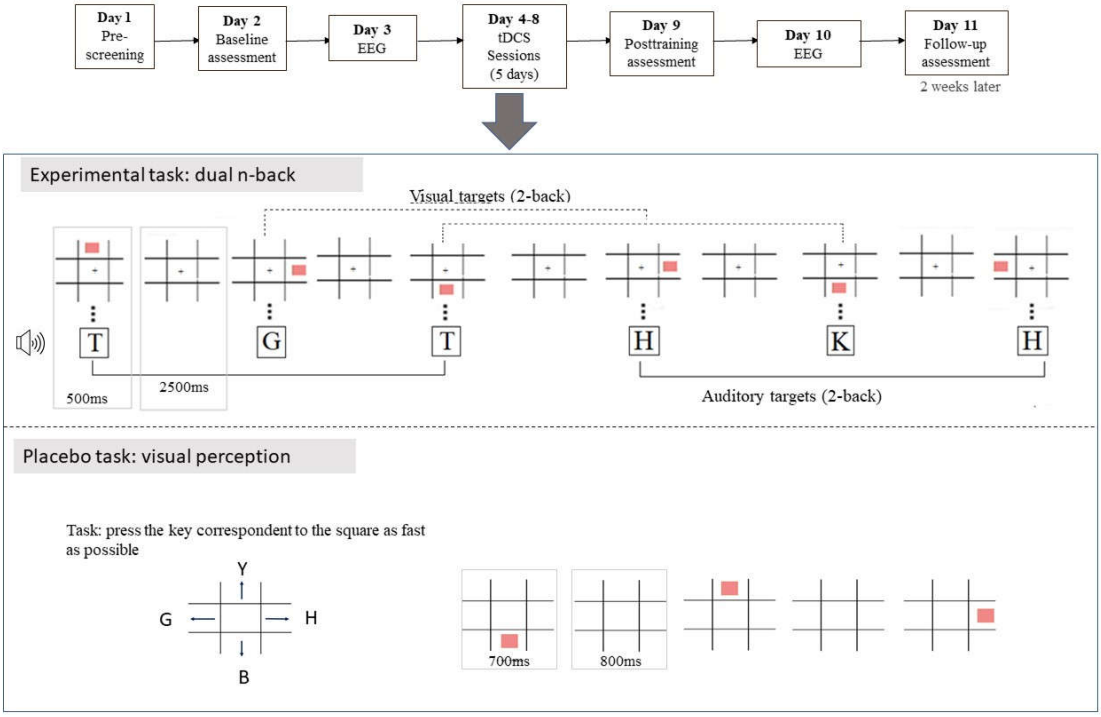

Figure 2. Schematic representation of the sessions. The experimental task was illustrated for a 2-back condition. *Note.* Participants underwent an EEG session, the results of which will be discussed in another manuscript.

Screening session

Participants completed a socioeconomic and medical questionnaire, the Jaeger Card (Kniestedt & Stamper, 2003), auditory discrimination of letters, GAI (Pachana et al., 2007; Ribeiro, Paúlac, Simoes, & Firmino, 2011), GDS (Pocinho et al., 2009; Yesavage et al., 1982), and MoCA (Freitas et al., 2011; Nasreddine et al., 2005).

Pretest

In this session, participants performed the vocabulary, the digit span and digit-symbol Coding of Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 2008), Raven's Advanced Progressive Matrices (RAPM) (Raven, Raven, & Court, 1998), Corsi Block-Tapping Test (Corsi, 1973), and the dual n-back task.

Training

Pergherm Wittevrongel, Tournoy, Schoenmakers, & Van Hulle (2018) demonstrated that 5 days of WMT were sufficient to improve n-back performance in elderly participants and no difference was observed between five or ten days of training. Accordingly, in the current study a total of 5 sessions were administered, although our experimental design has some differences from that study.

Participants answered a Visual Analogue Scale (VAS) to assesses possible tDCS side effects (i.e., levels of discomfort, fatigue, anxiety, pain, itching, humor, tingling, headache and sleepiness), before and after each day of intervention. Blinding was assessed in the last session using a questionnaire asking which condition participants thought they were allocated regarding task and tDCS.

Posttest and 15-days follow-up

In these sessions, participants performed the digit-symbol code, digit span, RAPM, Corsi Block-Tapping Test, and the dual n-back.

tDCS parameters

tDCS was applied during 20 minutes with an intensity of 2 mA, using two 5x7 cm2 saline-soaked electrode sponges (current density approximately 0.0057 mA/cm2) with anode positioned over the left DLPFC (F3) and the cathode over the contralateral supraorbital area (Fp2) (Jasper, 1958). The current fade in and fade out was 15/15 seconds. The electrode setup was identical for sham condition. However, the stimulation was discontinued after 45 sec of administration (15 sec of fade in/stimulation/fade out). Participants started the task after 3 minutes of tDCS.

Trained tasks

Experimental task

The task was displayed using the Presentation software package (Neurobehavioral Systems, Albany, CA). Participants were simultaneously shown visuospatial and auditory-verbal stimuli. The visuospatial stimulus was a square presented in one of eight possible locations in a 3x3 grid with a fixation cross on the central square. The auditory-verbal stimulus was one of nine possible consonants (T, G, X, H, R, S, L, K, J) displayed in a random order, delivered binaurally through Sony MDR-NC6 noise cancelling headphones. Stimuli were presented for 500 ms, with 2500 ms of interstimulus interval. For each trial, participants decided whether the stimulus presented was the same presented n trials before. Participants were instructed to press the 'spacebar' every time either a visuospatial or an auditory-verbal target was presented. At the end of each block, a feedback with the participant's hits was shown. The task consisted of 12 blocks with 25 trials each. In each block, there were 2 auditory-verbal and 2 visuospatial targets, and 1 stimulus that was a target in both modalities. The n level started with n = 1 and increased by 1 if the participants achieved 100% of hits in three consecutives blocks. During training, the n level started in the maximum level achieved by the participant in the previous day. However, if the number of hits in the last 3 blocks of the previous session was inferior to 60%, the n level was decreased by 1. Training lasted approximately 20 minutes per session.

Placebo task

A visuoperceptual task was used as placebo in order to control confounding variables resulting from the intervention setting and to allow the blinding. The task was presented in Superlab software (The Experimental Laboratory Software, version 5.0.3; Cedrus Corporation, San Pedro, CA). In this task, a 3x3 grid was presented with a fixation cross in the center. Squares were presented in one of four possible locations in the grid. Participants had to press the key ('t'; 'f'; 'v'; 'g' – marked with arrows), correspondent to the position where the square showed up. In total, there were 203 trials. Stimuli duration was 700 ms, with 800 ms of interstimulus interval.

Transfer measures are important to verify the generalization of the stimulation for other tasks not trained. Therefore, we used transfer tasks to be described in the next sections.

Near transfer tasks

Digit span

Participants listened to a sequence of digits and were instructed to recall them in the forward and backward order.

Corsi block-tapping test

In a board with nine blocks, participants reproduced a sequence of movements in the forward or backward order.

In both near transfer tasks, the first two trials consisted of 2 digits, and the length of the sequence increased by 1 every 2 trials until the participant had two consecutive errors at the same level. The outcome was the total number of sequences correctly recalled in the forward and backward modalities separately (maximum score of 16 for each task and order).

Far transfer tasks

RAPM

RAPM (set 1 and 2) (Raven et al., 1998) is composed by 48 figures with a 3x3 matrix of line and geometrical shapes, in which one of the shapes is missing. By choosing from eight options, participants were asked to complete the missing part from the figure. Two parallel forms were set by separating odd and even trials. The versions were randomized and counterbalanced between sessions in a way that in pretest and follow-up participants used one form, while in the posttest they performed the other version. Outcome was the sum of correct responses (one point for each/ maximum score of 6 points for set 1 and 18 for set 2).

Digit-symbol code

Participants completed as fast and accurately as possible digit-symbol correspondences during 120 sec, following a key provided in the top of the page. Total score is the number of correctly identified pairs. Maximum score is 133.

Digit-symbol Code was performed in order to assess gains in processing speed. . Gains in processing speed were expected in all three conditions, since the control group also executed a task

that targeted this domain. This task was used to control if gains observed in experimental conditions would be restricted to gains in WM and reasoning

Data analysis

Statistical analyses were conducted using RStudio, version 3.5.2 (R Core Team, 2018), with the following package: lme4 (Bates, Maechler, Bolker, & Walker, 2015); lmerTest (Kuznetsova, Brockhoff, & Christensen, 2017); glmmTMB (Brooks et al., 2017); brms (Bürkner, 2017); ordinal (Christensen, 2019); effects (Fox & Weisberg, 2018) and lsmeans (Lenth, 2016). Mixed-effects models were used due to their flexibility and efficiency in analysing repeated measures, accounting for pretest-differences in the outcomes (Winter, 2013). Level of significance was set at $p < 0.05$. We supported our results with Bayesian analysis. The effects were interpreted as significant only when the Bayesian analysis confirmed the frequentist results (Dienes, 2011).

The models were analysed to verify the relationship between each transfer outcome, in the three testing assessment sessions, considering the stimulation condition. As fixed effects, we entered the interaction group*moment into the model and participants as random effects. The performance of the trained task (probability of maximum level achieved across the 5 days of training) of the WMT+atDCS and WMT+stDCS groups was assessed with a similar modelling approach; however, in this case the "moment" variable was considered a continuous variable (from 1 to 5).

To verify whether near transfer gains predicted far transfer gains (Melby-Lervåg et al., 2016), we ran linear mixed models (LMMs) analyses with the RAPM set_1 scores of the atDCS+WMT group, having the gains for near transfer measures (i.e., forward and backward digit span and Corsi Block-Tapping Test) as fixed effect and participants as random effect. Gains were calculated as the difference between posttest/follow-up and pretest scores.

In the individual difference analysis, we added the predictors (age, educational level, general cognitive ability operationalised by RAPM-set 2, and vocabulary scores at baseline) as fixed effect, in the 3-way interaction: RAPM-set1~group*testing session*predictor. As random effects, we had intercepts for participants.

The effect sizes of post-intervention/follow-up were calculated using the package "metafor" (Viechtbauer, 2010), taken into consideration the pretest performance. They were calculated using

Hedges' g (Hedges, 1989) formula presented by Morris (2008), in formula 5, with a bias correction presented in formula 22.

All outcomes were dichotomous (blinding; gender), ordered (the maximum level achieved during training), or discrete variables (task scores). For dichotomous outcomes we performed logistic models (binomial distribution), for ordered categorical data we conducted ordered logit models, and for the remaining outcomes (discrete) we performed Conway-Maxwell-Poisson models. The ordered logit models were obtained with the R package "ordinal" (Christensen, 2019) and all the other were obtained with the R package "glmmTMB" (Brooks et al., 2017). Bayesian models used the default four Markov chains, with 2000 iterations per chain (including warmup). Finally, in the analysis where we verified if near transfer gains predicted far transfer gains, a transformation of the variables was made: after computing the difference between posttest/follow-up and pretest scores, a constant was added to the each variable.

Results[7]

Self-report side effects

Only small side effects (i.e., skin redness, small burning sensation and itching) were reported following stimulation. There was no group difference between VAS after/ before tDCS across groups in all sessions, except for the fourth session, in which the double-sham group presented higher score compared to atDCS (see supplementary Table S7).

Trained task

Supplementary figures S1 and S2 shows the raw data of dual n-back maximum level for WMT+atDCS and WMT+stDCS groups in each training day and the fitted data respectively. Training had a positive effect on the performance of the participants of both groups, since between two consecutive sessions the odds to falling into or below a given level (i.e., 1,2,3,4) increased about three times (exp (1.09) = 2.97, $p < .001$), i.e., rating in higher levels was more likely along the sessions. There is an effect of group, in which at the baseline, the odds of achieving a given level versus its lower levels are

[7] Supplementary Table S4 presents the correlations between pretest and posttest, and between pretest and follow-up outcomes.

about 18 times higher for WMT+stDCS (exp(2.89) = 17.99, p = .0452), compared with WMT+atDCS group. However, there is no interaction effect of group*time (estimate = 1.11 = exp(0.10), p = .75).

In short, both groups improved during the training with no significant difference between them, although the WMT+stDCS group already started the training achieving a higher level than the WMT+atDCS.

Transfer measures

Transfer results are described for each outcome in the following sequence: first, between-moments significant differences were listed for each group (see also Figure 3 and Table 1); second, for each moment, between-groups differences are highlighted (see also Figure 3 and Table 2); third, we presented the Hedges' g for each analysis (see supplementary Table S3).

In supplementary data, we display the Table S2 for descriptive statistics.

RAPM_set 1.

LMM showed a significant difference between pretest and posttest/follow-up only for the atDCS+WMT group. However, in each moment, no significant group differences were observed.

The Hedges' g for group differences between atDCS+WMT and stDCS+WMT were medium at both posttest and follow-up. In the case of the comparison between atDCS+WMT vs. double-sham, the effect size was medium at posttest but small at follow-up. Thererefore, atDCS+WMT outperformed both groups in posttest and follow-up. Regarding stDCS+WMT vs. the double-sham, the former displayed lower transfer effects in both moments.

In general, for this outcome, the gains were restricted to the atDCS+WMT condition.

RAPM_set 2.

LMMs showed a difference between pretest and posttest for the double-sham group, in which the performance of this group worsened. Regarding the differences between groups, the stDCS+WMT outperformed the double-sham at posttest and follow-up. atDCS+WMT started with a lower performance compared to the stDCS+WMT at pretest, however such difference was no longer significant at posttest/follow-up, indicating an improvement in that group.

Hedges' g for group differences between atDCS+WMT and stDCS+WMT were small at posttest and follow-up. For the comparison between atDCS+WMT vs. double-sham, the effect size was large at posttest (also the confidence interval did not include 0) and medium at follow-up, showing that transfer effects were superior in atDCS+WMT compared to the two other groups at posttest and follow-up. Comparing stDCS+ WMT vs. the double-sham, the Hedge' s was medium at both moments.

In general, stDCS+WMT presented less effect in RAPM_set2 compared to atDCS+WMT, yet greater effect when compared to the double-sham.

Digit-symbol coding.

LMMs showed significant differences between pretest and posttest/follow-up for the three groups. No between-groups differences were observed in any moment.

atDCS+WMT had a smaller effect than the stDCS+WMT at posttest and follow-up, and the same when comparing with the double-sham. Comparing stDCS+WMT vs. the double-sham, the effect sizes were closer to zero.

In general, all groups improved in this outcome, but the group who received atDCS yielded the smaller effect.

Forward digit span

LMMs showed a difference between the pretest and the follow-up only for the atDCS+WMT group. With respect to the group differences, in each training session, atDCS+WMT performed lower than the double-sham group. This difference was marginally significant in the posttest (but supported by Bayesian Analysis) and got non-significant at follow-up.

atDCS+WMT had a superior small Hedges' g compared to the stDCS+WMT at posttest and follow-up. When compared to the double-sham, the difference was closer to zero at posttest and small at follow-up. Comparing stDCS+WMT versus the double-sham, the effect sizes were closer to zero.

Overall, the effects were restricted to the atDCS+WMT.

Backward digit span

LMMs showed a difference between pretest and posttest/follow-up for the WMT+stDCS group. Regarding the differences between groups, the performance of the double-sham group was superior than the other two groups at follow-up.

atDCS+WMT demonstrated a superior small Hedges' g compared to the stDCS+WMT at posttest and a medium effect size at follow-up. When comparing with the double-sham, the effect was closer to zero at posttest and small at follow-up. In the case of stDCS+WMT vs. the double-sham, the effect sizes were always negative.

In sum, the effect was an unexpected decline of stDCS+WMT at posttest and follow-up.

Forward corsi block-tapping test.

LMMs showed no difference between-moments in any of the groups. Regarding between-groups differences, stDCS+WMT had a better performance than the double-sham group, however this difference became non-significant at follow-up.

Regarding the effect sizes, atDCS+WMT had lower effect size than the stDCS+WMT at posttest and follow-up. However, when compared to the double-sham, it had a superior small effect at posttest, which got closer to zero at follow-up. Comparing stDCS+WMT vs. the double-sham, the effect sizes were large at posttest, but small at follow-up.

In sum, stDCS+WMT group stood out due to their gains at posttest, however these gains were much smaller at follow-up.

Backward corsi block-tapping test.

LMMs showed a difference between pretest and follow-up for atDCS+WMT group and for the double-sham group. No difference between-groups was observed in any of the moments.

atDCS+WMT had a small effect compared to the stDCS+WMT at posttest but approached zero at follow-up. The comparison between atDCS+WMT and the double-sham was closer to zero. In the context of stDCS+WMT vs. the double-sham, the Hedges' g was small at posttest and approached zero at follow-up.

As improvement was observed in all groups, these results seem to be due to practice effects.

Table 1

Generalized Multilevel Models Results for each Moment per Group

			Frequentist analysis			Bayesian analysis				
Outcome	Group	Moment Comparison	Estimate	SE	*p*-value	Estimate	EE	CI	ER	PP
RAPM_set 1	atDCS+WMT	Posttest – Pretest	0.23	0.13	.076^	0.20	0.12	[.01, ∞[	22.67	.96*
		Follow-up – Pretest	0.25	0.13	.047*	0.22	0.12	[.03, ∞[	32.61	.97*
		Follow-up – Posttest	0.02	0.12	.834	0.02	0.11	[.03, ∞[	1.32	.57
	stDCS+WMT	Posttest – Pretest	-0.02	0.12	.884	-0.02	0.11	[.03, ∞[	1.31	.57
		Follow-up – Pretest	0.01	0.11	.909	0.02	0.11	[.03, ∞[	1.27	.56
		Follow-up – Posttest	0.03	0.12	.795	0.03	0.11	[.03, ∞[	1.64	.62
	Double-sham	Posttest – Pretest	0.00	0.13	.987	0.00	0.11	[.03, ∞[	1.00	.50
		Follow-up – Pretest	0.14	0.12	.238	0.13	0.11	[.03, ∞[	7.49	.88
		Follow-up – Posttest	0.14	0.12	.232	0.13	0.11	[.03, ∞[	8.78	.90
RAPM_set 2	atDCS+WMT	Posttest – Pretest	0.09	0.16	.597	0.08	0.17	[-.02, ∞[	2.22	.69
		Follow-up – Pretest	0.18	0.16	.254	0.17	0.16	[-.09, ∞[	5.62	.85
		Follow-up – Posttest	0.09	0.15	.539	0.09	0.16	[.17, ∞[	2.57	.72
	WMT+stDCS	Posttest – Pretest	-0.12	0.14	.418	-0.11	0.15	]-∞ , .13]	3.48	.78
		Follow-up – Pretest	0.06	0.14	.670	0.06	0.14	[-.17, ∞[	1.98	.66
		Follow-up – Posttest	0.17	0.14	.217	0.17	0.15	[-.06, ∞[	7.40	.88
	Double-Placebo	Posttest – Pretest	-0.36	0.18	.041*	-0.36	0.18	]-∞ , -.07]	49.00	.98*
		Follow-up – Pretest	-0.17	0.17	.305	-0.17	0.18	]-∞ , .12]	4.76	.83
		Follow-up – Posttest	0.19	0.18	.300	0.19	0.19	[-.12, ∞[	5.58	.85
SDC	WMT+atDCS	Posttest – Pretest	0.09	0.04	.035*	0.09	0.04	[.02, ∞[	58.70	.98*
		Follow-up – Pretest	0.17	0.04	<.001***	0.17	0.04	[.10, ∞[	∞	1.0*
		Follow-up – Posttest	0.08	0.04	.054^	0.08	0.04	[.01, ∞[	33.48	.97*
	WMT+stDCS	Posttest – Pretest	0.16	0.04	<.001***	0.16	0.04	[.09, ∞[	∞	1.0*
		Follow-up – Pretest	0.23	0.04	<.001***	0.23	0.04	[.16, ∞[	∞	1.0*
		Follow-up – Posttest	0.07	0.04	.060^	0.07	0.04	[.01, ∞[	32.06	.97*
	Double-sham	Posttest – Pretest	0.12	0.04	.005**	0.12	0.05	[.05, ∞[	284.71	1.0*
		Follow-up – Pretest	0.20	0.04	<.001***	0.20	0.04	[.13, ∞[	∞	1.0*
		Follow-up – Posttest	0.08	0.04	.063^	0.08	0.04	[.00, ∞[	22.53	.96*
Backward DS	WMT+atDCS	Posttest – Pretest	0.02	0.07	.734	0.02	0.07	[-.09, ∞[	1.73	.63
		Follow-up – Pretest	0.03	0.07	.612	0.03	0.06	[-.07, ∞[	2.24	.69
		Follow-up – Posttest	0.01	0.07	.870	0.01	0.06	[-.09, ∞[	1.30	.57
	WMT+stDCS	Posttest – Pretest	-0.14	0.07	.029*	-0.13	0.06	]-∞ , -.03]	51.63	.98*
		Follow-up – Pretest	-0.17	0.07	.012*	-0.15	0.07	]-∞ , -.05]	116.65	.99*
		Follow-up – Posttest	-0.02	0.07	.736	-0.02	0.07	]-∞ , .09]	1.62	.62
	Double-sham	Posttest – Pretest	0.02	0.06	.750	0.02	0.06	[-.08, ∞[	1.59	.61
		Follow-up – Pretest	0.04	0.06	.177	0.08	0.06	[-.02, ∞[	10.14	.91
		Follow-up – Posttest	0.06	0.06	.301	0.06	0.06	[-.04, ∞[	5.16	.84
Forward DS	WMT+atDCS	Posttest – Pretest	0.06	0.04	.163	0.06	0.04	[-.02, ∞[	9.67	.91
		Follow-up – Pretest	0.09	0.04	.038*	0.08	0.04	[.01, ∞[	42.48	.98*

Table 1. (cont.).

		Follow-up – Posttest	0.03	0.04	.497	0.03	0.04	[-.04, ∞[	2.86	.74
	WMT+stDCS	Posttest – Pretest	0.01	0.04	.865	0.01	0.04	[-.06, ∞[	1.26	.56
		Follow-up – Pretest	0.03	0.04	.503	0.03	0.04	[-.04, ∞[	2.75	.73
		Follow-up – Posttest	0.03	0.04	.618	0.02	0.04	[-.05, ∞[	2.12	.68
	Double-sham	Posttest – Pretest	0.04	0.04	.329	0.04	0.04	[-.03, ∞[	4.85	.83
		Follow-up – Pretest	0.05	0.04	.252	0.04	0.04	[-.02, ∞[	6.37	.86
		Follow-up – Posttest	0.01	0.04	.865	0.01	0.04	[-.06, ∞[	1.24	.55
Backward CBT	WMT+atDCS	Posttest – Pretest	0.02	0.07	.773	0.02	0.07	[-.10, ∞[	1.60	.62
		Follow-up – Pretest	0.13	0.07	.055^	0.13	0.07	[.01, ∞[	29.30	.97*
		Follow-up – Posttest	0.11	0.07	.103	0.11	0.07	[-.01, ∞[	15.06	.94
	WMT+stDCS	Posttest – Pretest	0.10	0.07	.153	0.10	0.07	[-.02, ∞[	11.62	.92
		Follow-up – Pretest	0.11	0.07	.119	0.10	0.07	[-.01, ∞[	13.23	.93
		Follow-up – Posttest	0.01	0.07	.896	0.01	0.07	[-.10, ∞[	1.18	.54
	Double-sham	Posttest – Pretest	0.07	0.07	.307	0.07	0.07	[-.05, ∞[	5.53	.85
		Follow-up – Pretest	0.14	0.07	.049*	0.13	0.07	[.02, ∞[	37.10	.97*
		Follow-up – Posttest	0.07	0.07	.344	0.06	0.06	[-.04, ∞[	5.24	.84
Forward CBT	WMT+atDCS	Posttest – Pretest	-0.01	0.05	.882	-0.01	0.05	]-∞ , .08]	1.23	.55
		Follow-up – Pretest	0.01	0.05	.885	0.01	0.05	[-.08, ∞[	1.25	.56
		Follow-up – Posttest	0.02	0.05	.769	0.01	0.05	[-.07, ∞[	1.55	.61
	WMT+stDCS	Posttest – Pretest	0.07	0.05	.188	0.06	0.05	[-.02, ∞[	8.80	.90
		Follow-up – Pretest	0.04	0.05	.457	0.04	0.05	[-.05, ∞[	3.21	.76
		Follow-up – Posttest	-0.03	0.05	.567	-0.03	0.05	]-∞ , .05]	2.57	.72
	Double-sham	Posttest – Pretest	-0.06	0.05	.297	-0.05	0.05	]-∞ , .03]	5.60	.85
		Follow-up – Pretest	-0.01	0.05	.885	-0.01	0.05	]-∞ , .08]	1.27	.56
		Follow-up – Posttest	0.05	0.05	.369	0.04	0.05	[-.04, ∞[	4.17	.81

Note. ^$p < .1$, *$p < .05$. PPS $\geq .95$. Significant values in bold. CI – 95% credible interval. Abbreviations. CBT = Backward Corsi Block-Tapping; DS = Digit span; EE = Estimate error; ER = Evidence Ratio; PP = Posterior probability; RAPM = Raven's Advanced Progressive Matrices; SDC = Digit- Symbol Code; SE = Standard Error.

Table 2

Generalized Multilevel Models Results for Between Group Analysis per Moment

			Frequentist analysis			Bayesian analysis				
Outcome	Moment	Group comparison	Estimate	SE	p-value	Estimate	EE	CI	ER	PPS
RAPM_set 1	Pretest	WMT+stDCS – WMT+atDCS	0.28	0.18	.118	0.24	0.17	[-.04, ∞[	11.86	.92
		Double-sham – WMT+atDCS	0.15	0.18	.401	0.13	0.17	[-.16, ∞[	3.41	.77
		Double-sham – WMT+stDCS	-0.13	0.17	.468	-0.11	0.16	]-∞ , .15]	3.03	.75
	Posttest	WMT+stDCS – WMT+atDCS	0.03	0.17	.843	0.02	0.17	[-.25, ∞[	1.22	.55
		Double-sham – WMT+atDCS	-0.08	0.17	.660	-0.07	0.17	]-∞ , .20]	2.01	.67
		Double-sham – WMT+stDCS	-0.11	0.17	.524	-0.09	0.16	]-∞ , .18]	2.48	.71
	Follow-up	WMT+stDCS – WMT+atDCS	0.04	0.17	.818	0.04	0.16	[-.23, ∞[	1.41	.59
		Double-sham – WMT+atDCS	0.04	0.17	.802	0.04	0.16	[-.22, ∞[	1.55	.61
		Double-sham – WMT+stDCS	0.00	0.17	.983	0.01	0.16	[-.26, ∞[	1.12	.53
RAPM_set 2	Pretest	WMT+stDCS – WMT+atDCS	0.41	0.23	.076^	0.39	0.24	[.00, ∞[	19.94	.95*
		Double-sham – WMT+atDCS	0.16	0.24	.500	0.16	0.25	[-.26, ∞[	2.71	.73
		Double-sham – WMT+stDCS	-0.25	0.23	.272	-0.24	0.24	]-∞ , .16]	5.46	.85
	Posttest	WMT+stDCS – WMT+atDCS	0.21	0.23	.365	0.20	0.24	[-.20, ∞[	4.01	.80
		Double-sham – WMT+atDCS	-0.29	0.25	.243	-0.28	0.26	]-∞ , .14]	6.72	.87
		Double-sham – WMT+stDCS	-0.50	0.24	.040*	-0.48	0.25	]-∞ , -.08]	38.60	.97*
	Follow-up	WMT+stDCS – WMT+atDCS	0.29	0.22	.199	0.28	0.24	[-.11, ∞[	7.95	.89
		Double-sham – WMT+atDCS	-0.19	0.24	.418	-0.19	0.25	]-∞, .22]	3.28	.77
		Double-sham – WMT+stDCS	-0.48	0.23	.038*	-0.47	0.24	]-∞ , -.08]	39.40	.98*
SDC	Pretest	WMT+stDCS – WMT+atDCS	0.10	0.11	.377	0.11	0.12	[-.09, ∞[	5.18	.84
		Double-sham – WMT+atDCS	-0.01	0.12	.923	0.00	0.12	]-∞ , .20]	0.92	.48
		Double-sham – WMT+stDCS	-0.11	0.11	.328	-0.11	0.12	]-∞, .08]	4.56	.82
	Posttest	WMT+stDCS – WMT+atDCS	0.17	0.11	.137	0.18	0.12	[-.01, ∞[	15.60	.94
		Double-sham – WMT+atDCS	0.02	0.11	.857	0.04	0.12	[-.16, ∞[	1.63	.62
		Double-sham – WMT+stDCS	-0.15	0.11	.191	-0.14	0.12	]-∞ , .05]	7.99	.89
	Follow-up	WMT+stDCS – WMT+atDCS	0.16	0.11	.153	0.17	0.12	[-.02, ∞[	13.98	.93
		Double-sham – WMT+atDCS	0.02	0.11	.872	0.03	0.12	[-.16, ∞[	1.65	.62
		Double-sham – WMT+stDCS	-0.14	0.11	.205	-0.14	0.12	]-∞ , .05]	8.07	.89
Backward DS	Pretest	WMT+stDCS – WMT+atDCS	0.18	0.11	.100	0.17	0.11	[-.01, ∞[	15.95	.94
		Double-sham – WMT+atDCS	0.16	0.11	.143	0.15	0.11	[-.02, ∞[	11.99	.92
		Double-sham – WMT+stDCS	-0.02	0.11	.858	-0.02	0.11	]-∞ , .15]	1.28	.56
	Posttest	WMT+stDCS – WMT+atDCS	0.02	0.11	.877	0.02	0.11	[-.16, ∞[	1.23	.55
		Double-sham – WMT+atDCS	0.16	0.11	.150	0.15	0.11	[-.03, ∞[	11.62	.92
		Double-sham – WMT+stDCS	0.14	0.11	.198	0.13	0.11	[-.05, ∞[	8.73	.90
	Follow-up	WMT+stDCS – WMT+atDCS	-0.02	0.11	.881	-0.02	0.11	]-∞ , .16]	1.26	.56
		Double-sham – WMT+atDCS	0.21	0.11	.054^	0.20	0.10	[-.03, ∞[	32.90	.97*
		Double-sham – WMT+stDCS	0.23	0.11	.038*	0.22	0.11	[-.04, ∞[	42.01	.98*
Forward DS	Pretest	WMT+stDCS – WMT+atDCS	0.09	0.07	.193	0.09	0.07	[-.03, ∞[	8.15	.89
		Double-sham – WMT+atDCS	0.15	0.07	.030*	0.14	0.07	[.03, ∞[	53.79	.98*

Table 2 *(cont..)*

		Double-sham – WMT+stDCS	0.06	0.07	.383	0.06	0.07	[-.06, ∞[	3.63	.78
	Posttest	WMT+stDCS – WMT+atDCS	0.04	0.07	.586	0.03	0.07	[-.08, ∞[	2.28	.69
		Double-sham – WMT+atDCS	0.13	0.07	.059^	0.12	0.07	[.01, ∞[	25.32	.96*
		Double-sham – WMT+stDCS	0.09	0.07	.179	0.09	0.07	[-.03, ∞[	8.37	.89
	Follow-up	WMT+stDCS – WMT+atDCS	0.03	0.07	.668	0.03	0.07	[-.09, ∞[	1.99	.66
		Double-sham – WMT+atDCS	0.11	0.07	.116	0.10	0.07	[-.01, ∞[	12.89	.93
		Double-sham – WMT+stDCS	0.08	0.07	.254	0.07	0.07	[-.04, ∞[	6.01	.86
Backward CBT	Pretest	WMT+stDCS – WMT+atDCS	-0.02	0.11	.828	-0.02	0.11	]-∞ , .16]	1.35	.57
		Double-sham – WMT+atDCS	-0.06	0.11	.617	-0.05	0.11	]-∞ , .14]	2.02	.67
		Double-sham – WMT+stDCS	-0.03	0.11	.777	-0.03	0.11	]-∞ , .15]	1.49	.60
	Posttest	WMT+stDCS – WMT+atDCS	0.06	0.11	.595	0.05	0.11	[-.12, ∞[	2.15	.68
		Double-sham – WMT+atDCS	0.00	0.11	.987	0.00	0.11	]-∞ , .18]	0.98	.50
		Double-sham – WMT+stDCS	-0.06	0.11	.585	-0.05	0.10	]-∞ , .12]	2.28	.70
	Follow-up	WMT+stDCS – WMT+atDCS	-0.05	0.11	.666	-0.05	0.11	]-∞ , .13]	1.98	.66
		Double-sham – WMT+atDCS	-0.05	0.11	.651	-0.04	0.11	]-∞ , .14]	1.89	.65
		Double-sham – WMT+stDCS	0.00	0.11	.984	0.00	0.11	]-∞ , .17]	0.95	.49
Forward CBT	Pretest	WMT+stDCS – WMT+atDCS	-0.02	0.07	.806	-0.02	0.06	]-∞ , .09]	1.45	.59
		Double-sham – WMT+atDCS	-0.02	0.07	.818	-0.01	0.06	]-∞ , .09]	1.42	.59
		Double-sham – WMT+stDCS	0.00	0.07	.988	0.00	0.07	[-.11, ∞[	1.04	.51
	Posttest	WMT+stDCS – WMT+atDCS	0.06	0.06	.360	0.05	0.06	[-.05, ∞[	4.04	.80
		Double-sham – WMT+atDCS	-0.06	0.07	.343	-0.06	0.07	]-∞ , .05]	4.71	.82
		Double-sham – WMT+stDCS	-0.12	0.07	.063^	-0.11	0.06	]-∞ , -.01]	28.2	.97*
	Follow-up	WMT+stDCS – WMT+atDCS	0.01	0.06	.818	0.01	0.06	]-∞ , .15]	1.37	.58
		Double-sham – WMT+atDCS	-0.03	0.07	.645	-0.03	0.06	[-.09, ∞[	2.04	.67
		Double-sham – WMT+stDCS	-0.04	0.06	.490	-0.04	0.06	]-∞ , .07]	2.97	.75

Note. ^$p < .1$, *$p < .05$. PPS≥..95. Significant values in bold. CI – 95% credible interval. Abbreviations. CBT = Backward Corsi Block-tapping Test; DS = Digit Span; EE = Estimate Error; ER = Evidence Ratio; PP = Posterior Probability; RAPM = Raven's Advanced Progressive Matrices; SDC = Digit-symbol Code; SE = Standard Error.

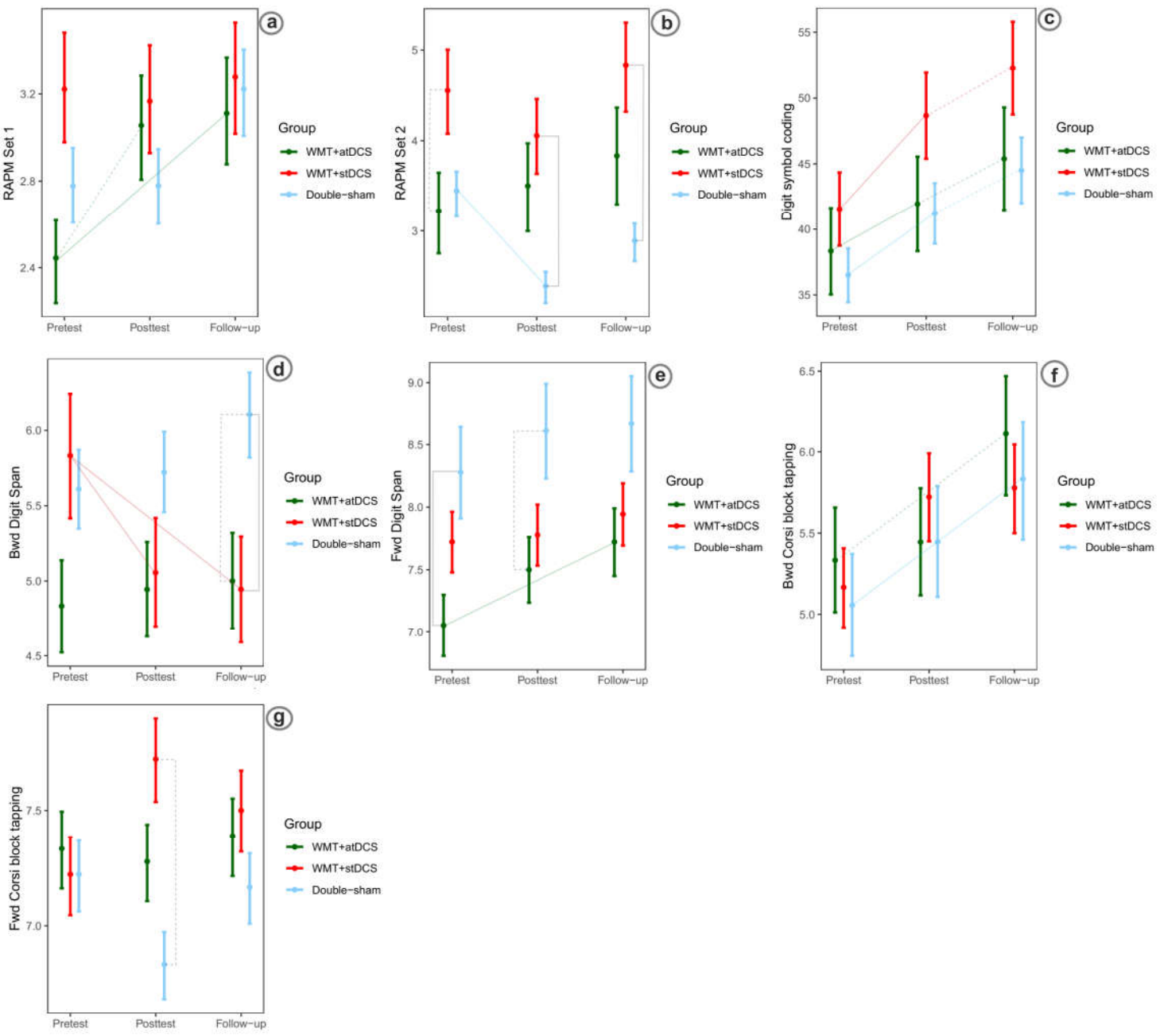

Figure 3. Fitted data representation of group x session interaction for each outcome. Solid lines represent statistically significant differences ($p < 0.05$), while dashed lines represent marginally significant results ($p < 0.1$) supported by Bayesian Analysis. *Notes.* RAPM set 1 (a); RAPM set 2 (b); Digit Symbol Coding (c); Backward Digit Span (d); Fwd Digit Span (e); Bwd Corsi block tapping (f); Fwd corsi block tapping (g); atDCS = active tDCS; stDCS = sham tDCS. *Abbreviations.* Bwd = Backward; Fwd = Forward; RAPM = Raven Advanced Progressive Matrices.

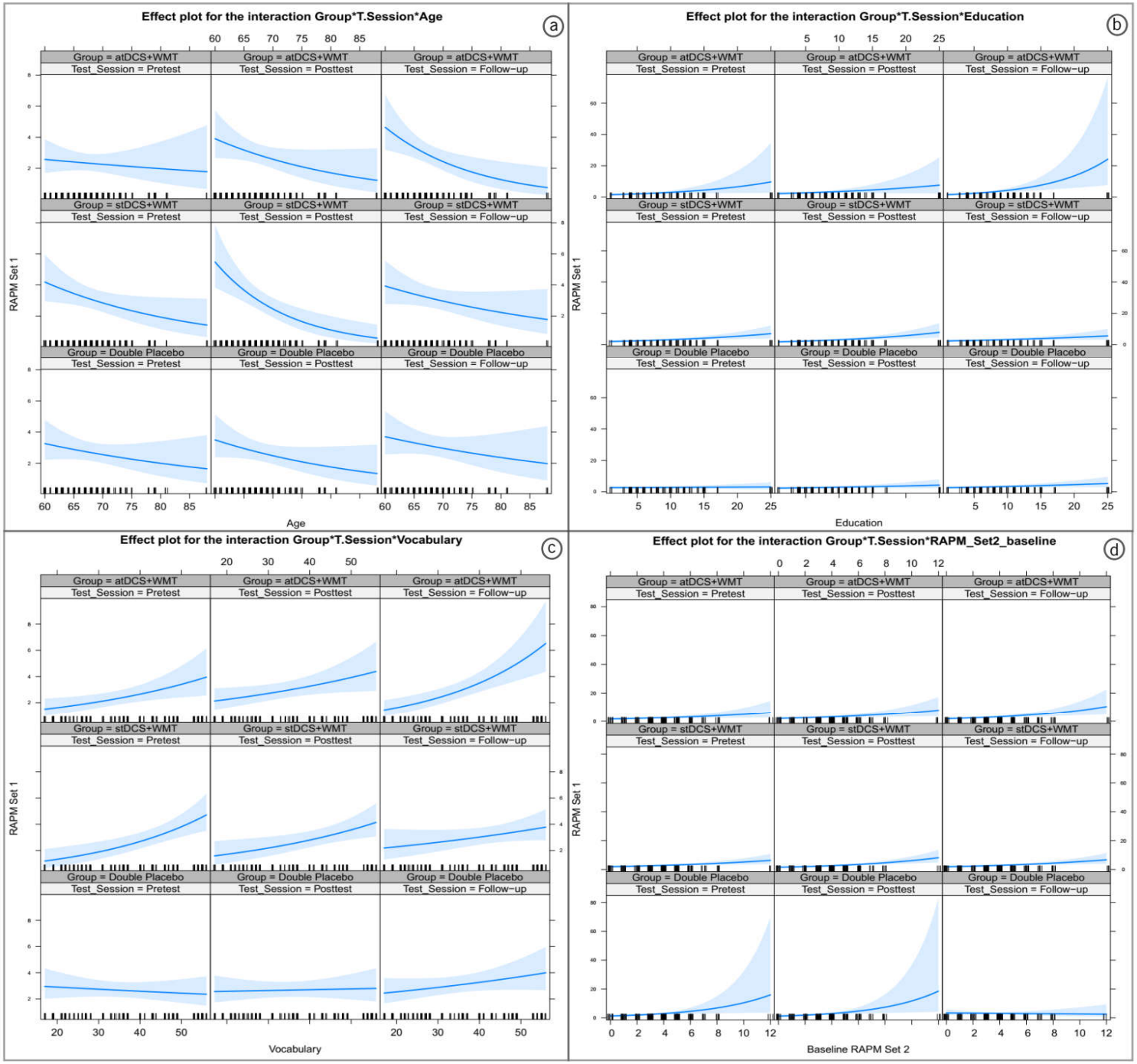

Figure 4. Fitted values (Group x Testing Session x Predictor) for each predictor in RAPM set 1 scores. *Notes.* Predictors: age (a); education (b); vocabulary (c); baseline RAPM set 2 (d). Shaded area is a pointwise 95% confidence band for the fitted values, based on standard errors and computed from the covariance matrix of the fitted regression coefficients.

Near transfer gains moderation of far transfer gains.

Gains in backward digit span were moderating gains on reasoning. No other analysis was significant (supplementary Table S6).

Individual differences prediction of transfer effects.

We verified if individual differences (i.e., general cognitive ability at pretest, measured by RAPM_set 2 and vocabulary; age; educational level) would influence the transfer effects for RAPM_set1 (See Figure 4 and supplementary Table S5). Although frequentist analysis suggested the influence of reasoning and vocabulary in WMT effects, the Bayesian Analysis did not confirm these results.

Discussion

In this study, we assessed the transfer effects of atDCS coupled with a WMT, compared to stDCS plus WMT or a double-sham condition, in untrained cognitive performance of healthy older adults, using LMMs complemented by Bayesian Analysis. Individual characteristics (i.e., years of formal education; baseline cognitive ability and RAPM scores; age) were also explored as putative predictors of transfer effects.

During training, both groups that performed the dual n-back task (WMT+atDCS; WMT+stDCS) improved throughout training sessions, having no significant difference between them. However, considering transfer effects, our data suggested that atDCS+WMT group presented more gains in reasoning and forward digit span in comparison with the other groups. In line with previous studies assessing WMT, those effects were stronger at follow-up (Borella, Cantarella, Carretti, De Lucia, & De Beni, 2019; Jaeggi, Buschkuehl, Shah, & Jonides, 2014), which may be due to "sleeper effect", meaning that improvements in some cognitive domains take longer to manifest, especially in the case of older adults. The transfer effects were partially consistent with Ruf et al. (2017) that observed near transfer effects after 3-days of DLPFC atDCS coupled with n-back task. However, other tDCS studies failed to find such transfer effects (Lawlor-Savage & Goghari, 2016; Nilsson et al., 2017). These differences among studies may be due to variations in experimental protocols. To illustrate it, Nilsson et al. (2017) had a longer protocol with 20 days of intervention, whereas for another study (Lawlor-Savage & Goghari, 2016), participants had training for 5 weeks, 5-days per week. In fact, a previous meta-

analysis on video-game training had shown that short-period trainings may be more effective than long-period trainings (Toril, Reales, & Ballesteros, 2014).

We observed that the stDCS+WMT group displayed superior gains in forward Corsi Block-Tapping Test in comparison to the double-sham, but these gains did not extend to follow-up. stDCS+WMT also outperformed the double-sham in RAPM_set 2. These results are in line with previous WMT experiments showing transfer effects of at posttest, yet small or no transfer effect at follow-up (Borella et al., 2017).

We observed no superiority of the experimental conditions in backward Corsi block-tapping test and digit span. Thus, our initial hypothesis was partially supported as the experimental conditions in contrast to the double-sham led to superior gains in the RAPM scores, but near transfer results were more controversial.

The fact that near transfer effects observed in the atDCS+WMT were restrict to forward digit span, not achieving improvement in Corsi Block-tapping Test, may be associated with the brain stimulated area (F3) and with the lateralization of verbal/visuospatial processing. Previous evidence have been highlighting the importance of laterality-dependence of stimulation by proposing the right DLPFC tDCS in the case of spatial tasks and left in the case of verbal stimuli (Ruf et al., 2017). Since visual WM decline is more accentuated in elderly people, right stimulation might be more advantageous (Cansino et al., 2013).

Interestingly enough, gains in WM performance predicted gains in reasoning, confirming the rationale that far transfer is dependent on near transfer gains (Melby-Lervåg et al., 2016). However, this relationship was restricted to backward digit span. The fact that it was limited to the backward modality is not surprising as it involves additional processing demands in comparison with the forward modality, which only requires simple retention of information (Zokaei, Burnett Heyes, Gorgoraptis, Budhdeo, & Husain, 2015). Again, the null results concerning the relationship between Corsi Block-tapping Test and far transfer may be due to the left stimulation.

As expected, all groups improved in processing speed, with the atDCS+WMT showing less improvement. Our team has previously reported that tDCS increased accuracy in a inhibition task with a speed-cost (Leite et al., 2018). Thus, this abovementioned result may be due to this speed-accuracy differentiation, with tDCS targeting accuracy.

Finally, we have not enough evidence to confirm that individual differences modulated transfer effects. However, further studies are necessary to verify the effects of age and vocabulary, since the frequentist analysis suggested those variables as possible moderators.

Overall, this study stands out by the analysis complemented by Bayesian methods and its experimental design, which had three conditions that allow to study the effects of tDCS and WMT separately. Instead of using a passive control group, we had an active control task. This allows to control for the effects resulting from social contact or participant´s expectations. The main limitation was the between-group difference at baseline. The atDCS had a worse performance in vocabulary, RAPM_set2 and forward digit span.

Conclusion

This work found that WMT associated with DLPFC atDCS may improve short-term memory and reasoning, showing evidence of the effectiveness of combining these techniques. Our results have practical implications, as we have demonstrated far transfer to reasoning, which is a construct associated with functioning in many aspects of life (Aichele, Rabbitt, & Ghisletta, 2015; Gottfredson & Deary, 2004; Neisser et al., 1996; Schmand, Smit, Geerlings, & Lindeboom, 1997).

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Appendix C

Supplementary material (study IV)

Supplementary Table S1.
Characterization of the sample

Measure	WMT+atDCS	WMT+stDCS	Double-sham	p-value	ER	PPS
Age	67.61 (5.11)	68.67 (6.98)	68.33 (5.82)	G2-G1: .583	2.41	.71
				G3-G1: .707	1.61	.62
				G3-G2: .863	1.36	.58
Gender (female/male)	14/4	13/5	14/4	G2-G1: .701	1.93	.66
				G3-G1: 1.00	1.00	.50
				G3-G2: .701	1.98	.66
Education (in years)	6.39 (3.26)	8.89 (5.74)	7 (5.95)	G2-G1: .101	16.86	.94
				G3-G1: .657	1.93	.66
				G3-G2: .231	7.02	.88
MoCa	22.5 (2.94)	23 (3.66)	22.56 (1.92)	G2-G1: .753	1.57	.61
				G3-G1: .972	1.02	.51
				G3-G2: .780	1.53	.60
GAI	3.72 (4.53)	3.11 (3.68)	3.67 (3.22)	G2-G1: .654	2.02	.67
				G3-G1: .970	1.05	.51
				G3-G2: .682	1.87	.65
GDS	4.72 (3.21)	3.56 (3.11)	3.06 (3.13)	G2-G1: .326	4.87	.83
				G3-G1: .138	14.75	.94
				G3-G2: .613	2.30	.70
Vocabulary	33.5 (12.30)	41.94 (12.26)	34.78 (11.72)	G2-G1: **.035***	40.24	**.98***
				G3-G1: .737	1.66	.62
				G3-G2: .076^	23.1	**.96***

Notes. Mean values with standard deviation in parentheses. *p<.05; ^p<.01. *PP≥.95. Abbreviations. ER = (Bayesian) Evidence Ratio; GAI = Geriatric Anxiety Inventory; GDS = Geriatric Depression Scale; MoCA = Montreal Cognitive Assessment; PP = Posterior probability; WMT = Working Memory Training; tDCS = Transcranial Direct Current Stimulation. The significance of the between-group differences was assessed through generalized modeling, using suitable probability distribution families (and corresponding statistical tests): binomial (gender, blinding_task, blinding_tDCS), negative binomial (Education, MoCa, GAI, GDS), and Conway-Maxwell-Poisson (in all the other cases). Bayesian analysis confirmed all significant and marginal significant frequentist results.

Supplementary Table S2.

Descriptive Statistics for the Outcome Measures by Group and Time-point (Pretest, Posttest, Follow-up).

		WMT + atDCS						WMT + stDCS						Double-sham					
		Pretest		Posttest		Follow-up		Pretest		Posttest		Follow-up		Pretest		Posttest		Follow-up	
Task	N	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
RAPM set 1	18	2.44	1.10	3.06	1.39	3.11	1.88	3.22	1.73	3.17	1.72	3.28	1.53	2.78	1.44	2.78	1.31	3.22	1.22
RAPM set 2	18	3.22	2.24	3.50	2.98	3.83	3.63	4.56	2.81	4.06	2.84	4.83	2.43	3.44	1.38	2.39	1.61	2.89	2.08
RAPM total	18	5.67	3.01	6.56	4.46	6.94	5.09	7.78	3.98	7.22	3.92	8.11	3.12	6.22	2.41	5.17	2.55	6.11	2.85
DSC	18	38.33	17.31	41.94	15.76	45.39	16.92	41.56	14.39	48.67	15.01	52.28	15.39	36.50	8.93	41.22	8.88	44.50	14.28
Fwd CBT	18	7.33	1.46	7.28	1.53	7.39	1.42	7.22	1.17	7.72	1.53	7.50	1.82	7.22	1.17	6.83	1.47	7.17	1.34
Fwd DS	18	7.06	1.43	7.50	1.54	7.72	1.56	7.72	1.60	7.78	1.56	7.94	1.30	8.28	2.05	8.61	1.88	8.67	2.28
Bwd CBT	18	5.33	2.06	5.44	2.48	6.11	1.71	5.17	1.34	5.72	1.81	5.78	1.44	5.06	1.98	5.44	2.45	5.83	1.54
Bwd DS	18	4.83	1.72	4.94	1.86	5.00	1.88	5.83	2.12	5.06	2.18	4.94	1.89	5.61	1.50	5.72	1.74	6.11	1.37

Note. Abbreviations. Fwd = Forward. Bwd = Backward. CBT = Corsi Block-Tapping Test t. DS= Digit Span. DSC = Digit Symbol-Coding.

Supplementary Table S3.

Hegde's g Corrected by Baseline for Posttest and Follow-up (Morris, 2008).

	atDCS+WMT *vs* stDCS+WMT		atDCS+WMT *vs* double-sham		stDCS+WMT *vs* double-sham	
	Posttest	Follow-up	Posttest	Follow-up	Posttest	Follow-up
RAPM set 1	0.56 (-0.12; 1.24)	0.55 (-0.07; 1.17)	0.53 (-0.16; 1.23)	0.29 (-0.39; 0.96)	-0.03 (-0.65; 0.58)	-0.26 (-0.92; 0.39)
RAPM set 2	0.29 (-0.26; 0.83)	0.17 (-0.34; 0.68)	0.85 (0.11; 1.59)	0.64 (-0.07; 1.36)	0.56 (-0.16; 1.28)	0.48 (-0.23; 1.19)
DSC	-0.27 (-0.65; 0.10)	-0.32 (-0.76; 0.12)	-0.31 (-0.70; 0.09)	-0.47 (-0.92; -0.01)	-0.03 (-0.47; 0.40)	-0.14 (-0.65; 0.36)
Bwd Digit Span	0.41 (-0.17; 0.99)	0.49 (-0.04; 1.02)	-0.01(-0.55; 0.54)	-0.23 (-0.85; 0.40)	-0.42 (-0.95; 0.10)	-0.72 (-1.29; -0.15)
Fwd Digit Span	0.26 (-0.34; 0.86)	0.31 (-0.36; 0.98)	0.14 (-0.38; 0.66)	0.26 (-0.35; 0.88)	-0.12 (-0.73; 0.48)	-0.05 (-0.67; 0.57)
Bwd CBT	-0.34 (-0.94; 0.26)	-0.07 (-0.53; 0.38)	-0.14 (-0.69; 0.41)	-0.01 (-0.57; 0.55)	0.21 (-0.31; 0.73)	0.06 (-0.49; 0.61)
Fwd CBT	-0.45 (-1.20; 0.31)	-0.19 (-0.93; 0.55)	0.28 (-0.50; 1.07)	0.08 (-0.56; 0.72)	0.73 (-0.06; 1.52)	0.27 (-0.48; 1.02)

Note. Confidence Interval between parentheses. Abbreviations. a-tDCS = active tDCS; CBT = Corsi-Block Tapping; DSC= Digit Symbol-Coding; s-tDCS = sham tDCS; WMT = Working memory training. Bwd = backward. Fwd = Forward. RAPM = Raven's Advanced Progressive Matrices.
STM = short-term memory. WM = Working memory.

Supplementary Table S4.

Pearson Correlation Coefficients of Transfer Measures Between Pretest and Posttest or Follow-up

	Pretest *vs* posttest			Pretest *vs* follow-up		
	tDCS + WM	Sham tDCS + WM	Double-sham	tDCS + WM	Sham tDCS + WM	Double-sham
Fwd Corsi-Block Tapping	0.35	0.37	0.23	0.53	0.19	0.50
Fwd Digit Span	0.70	0.47	0.68	0.53	0.47	0.64
Bwd Corsi-Block Tapping	0.55	0.65	0.76	0.77	0.81	0.56
Bwd Digit Span	0.58	0.66	0.72	0.60	0.79	0.51
RAPM set 1	0.41	0.58	0.54	0.60	0.58	0.43
RAPM set 2	0.63	0.69	0.23	0.71	0.70	0.16
Digit Symbol-Coding	0.88	0.85	0.83	0.87	0.85	0.86

Abbreviations. Bwd = backward. Fwd = Forward.

Supplementary Table S5.

Results of Mixed Model Analysis of individual differences.

		Frequentist analysis			Bayesian analysis				
Group	Moment comparison	Estimative	SE	*p*-value	Estimate	EE	CI	ER	PP
AGE (negbinomial)									
WMT + atDCS	Posttest – pretest	-0.03	0.03	.270	-0.03	0.04	]-∞ , .05]	3.01	.75
WMT + atDCS	Follow-up – pretest	-0.05	0.03	**.045***	-0.06	0.04	]-∞ , .01]	9.26	.90
WMT + atDCS	Follow-up – posttest	-0.02	0.02	.345	-0.03	0.04	]-∞ , .05]	2.69	.73
WMT + stDCS	Posttest – pretest	-0.04	0.02	.069^	-0.04	0.04	]-∞ , .02]	8.03	.89
WMT + stDCS	Follow-up – pretest	0.01	0.02	.618	0.01	0.03	[-.04, ∞[	1.64	.62
WMT + stDCS	Follow-up – posttest	0.05	0.02	**.022***	0.06	0.04	[0.00, ∞[	15.46	.94
EDUCATIONAL LEVEL (negbinomial)									
WMT + atDCS	Posttest – pretest	-0.03	0.04	.491	-0.02	0.01	]-∞ , .08]	1.95	.66
WMT + atDCS	Follow-up – pretest	0.04	0.04	.306	0.04	0.06	[-.06, ∞[	2.71	.73
WMT + atDCS	Follow-up – posttest	0.06	0.03	.066^	0.06	0.06	[-.03, ∞[	6.55	.87
WMT + stDCS	Posttest – pretest	0.01	0.02	.599	0.01	0.03	[-.04, ∞[	1.62	.62
WMT + stDCS	Follow-up – pretest	-0.02	0.02	.389	-0.02	0.03	]-∞ , .04]	2.25	.69
WMT + stDCS	Follow-up – posttest	-0.02	0.02	.349	-0.03	0.03	]-∞ , .03]	4.05	.80
VOCABULARY (negbinomial)									
WMT + atDCS	Posttest – pretest	-0.01	0.01	.585	-0.01	0.02	]-∞ , .03]	1.71	.63
WMT + atDCS	Follow-up – pretest	0.02	0.01	.149	0.02	0.02	[-.01, ∞[	4.26	.81
WMT + atDCS	Follow-up – posttest	0.02	0.01	.036*	0.02	0.02	[-.01, ∞[	8.43	.89
WMT + stDCS	Posttest – pretest	-0.01	0.01	.321	-0.01	0.02	]-∞ , .02]	2.78	.74
WMT + stDCS	Follow-up – pretest	-0.02	0.01	.043*	-0.02	0.02	]-∞ , .01]	7.58	.88
WMT + stDCS	Follow-up – posttest	-0.01	0.01	.300	-0.01	0.02	]-∞ , .02]	2.63	.72
RAVEN (negbinomial)									
WMT + atDCS	Posttest – pretest	-0.01	0.05	.837	-0.01	0.08	]-∞ , .12]	1.11	.53
WMT + atDCS	Follow-up – pretest	-0.01	0.05	.855	-0.01	0.08	]-∞ , .12]	1.19	.54
WMT + atDCS	Follow-up – posttest	0.00	0.04	.965	0.00	0.06	]-∞ , .09]	1.03	.51
WMT + stDCS	Posttest – pretest	0.01	0.04	.869	-0.01	0.07	]-∞ , .10]	1.22	.55
WMT + stDCS	Follow-up – pretest	-0.03	0.05	.472	-0.04	0.07	]-∞ , .08]	2.71	.73
WMT + stDCS	Follow-up – posttest	-0.04	0.05	.390	-0.04	0.07	]-∞ , .08]	2.29	.70

Note. *^p<.1, *p<.05, **p<.01, ***p<.001.* *PPS>.95. Significant values in bold. CI – 95% credible interval. EE – Estimate error. ER = Evidence ratio. PP – Posterior probability. SE – Standard Error

Supplementary Table S6.

Results of Mixed Model Analysis of Near Transfer Predicting Far Transfer Gains

Near transfer measure	Estimate	Standard Error	*p*-value	Estimate	EE	95%CI	ER	PP
DSBA	0.10	0.04	**.017***	0.09	0.04	[.02, ∞[	70.43	**.99***
DSFA	0.06	0.05	.207	0.06	0.05	[-.02, ∞[	7.89	.89
CBA	-0.02	0.03	.555	-0.02	0.03	]-∞, .03]	2..79	.74
CFA	-0.01	0.04	.738	-0.02	0.04	]-∞, .05]	2.02	.67

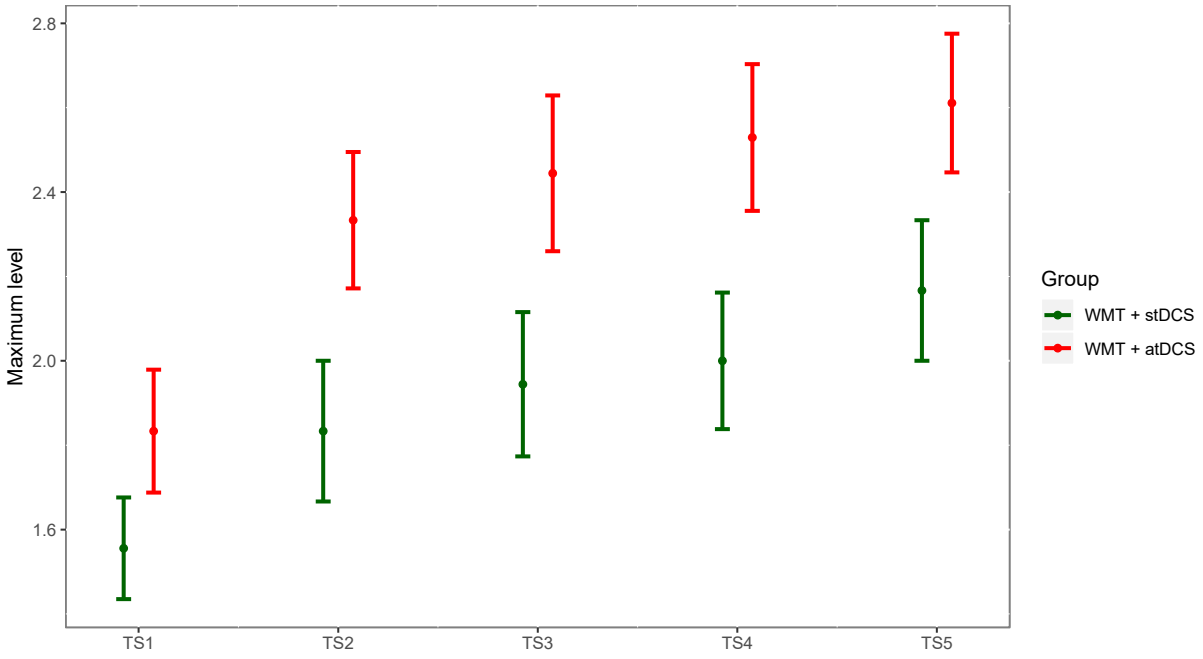
Note. **p*<.05. * PS>.95. . Significant values in bold. This analysis was performed only for the outcome RAPM_set 1, group WMT+atDCS. Abbreviations. EE = Estimate error. ER = evidence ratio. CI = 95% credible interval. PP = Posterior probability. CBT = Backward Corsi Block-Tapping. DS = Digit span. Bwd = backward. Fwd = Forward.

Supplementary Table S7.

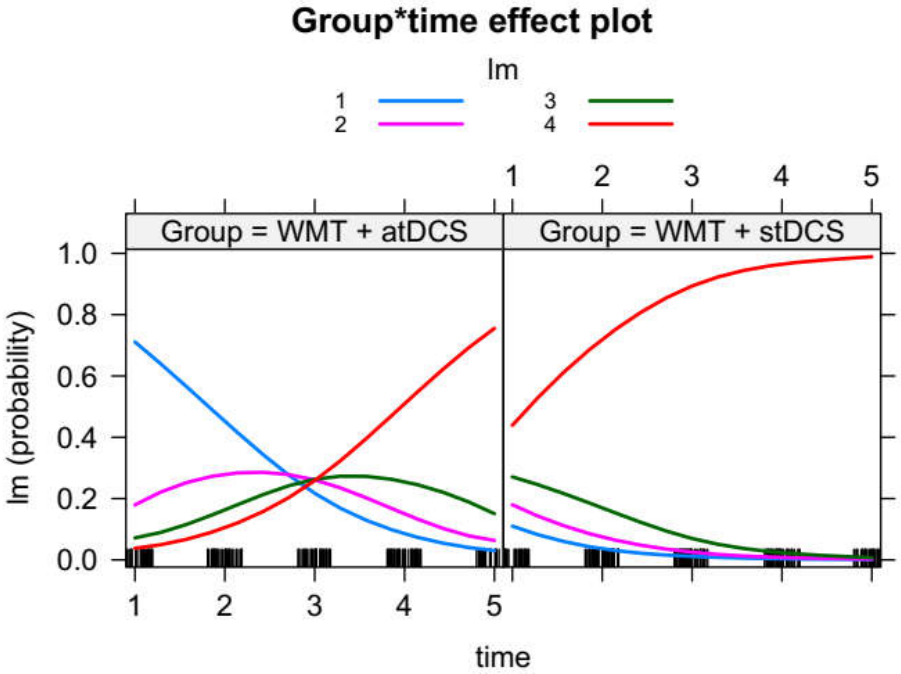
VAS pre and post-tDCS differences between groups for each tDCS session

			Frequentist Analysis			Bayesian Analysis				
Outcome	**Day**	**Group comparison**	**Estimate**	**SE**	***p*value**	**Estimate**	**EE**	**95%CI**	**ER**	**PP**
VAS	1	WMT+stDCS – WMT+atDCS	0.00	0.10	.985	0.00	0.10	[-∞ , .17]	1.05	.51
		double-sham – WMT+atDCS	-0.02	0.10	.825	-0.02	0.11	[-∞ , .16]	1.39	.58
		double-sham – WMT+stDCS	-0.02	0.10	.839	-0.02	0.11	[-∞ , .16]	1.34	.57
VAS	2	WMT+stDCS – WMT+atDCS	0.07	0.05	.137	0.07	0.05	[-.01, ∞]	11.78	.92
		double-sham – WMT+atDCS	0.07	0.05	.111	0.07	0.05	[-.01, ∞]	13.60	.93
		double-sham – WMT+stDCS	0.00	0.05	.917	0.00	0.05	[-.07, ∞]	1.19	.54
VAS	3	WMT+stDCS – WMT+atDCS	-0.02	0.05	.705	-0.02	0.06	[-∞ , .07]	1.86	.65
		double-sham – WMT+atDCS	-0.06	0.06	.247	-0.07	0.06	[-∞ , .03]	6.78	.87
		double-sham– WMT+stDCS	-0.04	0.06	.433	-0.04	0.06	[-∞ , .05]	3.57	.78
VAS	4	WMT+stDCS – WMT+atDCS	0.04	0.04	.306	0.04	0.04	[-.03, ∞]	5.16	.84
		double-sham – WMT+atDCS	0.08	0.04	.068^	0.07	0.04	[0.00, ∞]	23.39	**.96***
		double-sham– WMT+stDCS	0.03	0.04	.413	0.03	0.04	[-0.04, ∞]	3.53	.78
VAS	5	WMT+stDCS – WMT+atDCS	-0.03	0.03	.293	-0.04	0.03	[-∞ , .02]	5.29	.84
		double-sham – WMT+atDCS	-0.04	0.03	.213	-0.04	0.03	[-∞ , .01]	8.73	.90
		double-sham – WMT+stDCS	-0.01	0.03	.834	-0.01	0.03	[-∞ , .05]	1.36	.58

Note. ^*p*<.1. *PPS>.95. Significant values in bold. The outcome was analysed as a continuous variable since it was the sum of the individual items. Abbreviations. CI = 95% credible interval.EE = Estimate error. ER = Evidence ratio. PP = Posterior probability. VAS = Visual Analogue Scale.



Supplementary Figure S1. Dual n-back maximum level (raw data).



Supplementary Figure S2. Dual n-back maximum level (fitted data). This figure shows the probability of participants to achieve a level ≤1 (blue), ≤2 (pink), ≤3 (green) and ≤4 (red) in the groups WMT+atDCS (left) and WMT+stDCS (right) for each training day. Both groups increased the probability of achieving a level ≤4 along the sessions. However, WMT+stDCS started already with a high probability of achieve this level.

CHAPTER V

LATE ENDOGENOUS ERPs AS MARKERS FOR FLUID INTELLIGENCE IN OLDER ADULTS

Probing late endogenous ERP components as markers for fluid intelligence in healthy older adults[8]

Abstract

As world population ages, the number of age-related neurological diseases increases; and, consequently, the need for studies assessing brain activity indices of cognitive capacities in older populations that may ultimately be used to aid early diagnosis, as well as to guide individually-tailored intervention for these populations. While some Event-related potential (ERP) components, such as the P300 and late positive complex (LPC), have been associated with fluid intelligence (Gf) in young population; little is known whether this association holds for older people. Therefore, the main goal of this study was to assess whether these late endogenous ERP components are associated with Gf in the elderly. Hence, 57 healthy older adults performed a continuous performance task (CPT) and a visual oddball paradigm while EEG was recorded. Participants were organized into 2 groups, according to their performance in the Raven's Advanced Progressive Matrices test (RAPM), a proxy of Gf: Gf high-performance (HP) and Gf low-performance (LP). Results showed that the HP group, compared to the LP group, had significant higher amplitudes for LPC in the CPT and shorter P300 latencies in the oddball task. Furthermore, the RAPM scores were associated with these late endogenous ERP components. This study provides evidence for the role of ERP components, in particular the LPC amplitude, as an electrophysiological proxy of Gf abilities in the elderly.

Keywords: Event-related potentials (ERPs); P300; LPC; P200; CPT; oddball paradigm; reasoning; older people.

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[8]Publications derived from this study:

Peer reviewed publications in print or other media

Teixeira-Santos, A.C. Pinal, Pereira, D.R., Carvalho, S., & Sampaio A. (2019). Probing late endogenous ERP components as markers for fluid intelligence in healthy older adults. Manuscript in preparation.

Abstracts and Poster Presented at Academic Meetings in topics related to this chapter

Teixeira-Santos, A.C., Pinal, D, Pereira, D.R., Carvalho, S. & Sampaio, A. (2019). Evaluating the relationship of late endogenous ERP components and fluid intelligence in healthy older people. Poster session presented at the Alpine Brain Imaging Meeting, Champéry, Switzerland.

Introduction

The world population is getting older and it brings together the necessity to better understand and characterize the advancing age. In the cognitive domain, many aging-related changes, such as a reduction in fluid intelligence (Gf) are observed (Hartshorne & Germine, 2015; Salthouse, 2010). Individual differences among the elderly are also observed with some individuals performing in a high-level while others present a very poor performance (Schmitt, Wolff, Ferdinand, & Kray, 2014). Gf is the capacity of making analogies and solve original problems, independent of educational or sociocultural level (Jensen, 1998; Merrifield, 1975). Gf is further, a predictor of functioning in many aspects of life, such as social status, expected income, job performance, social outcomes, mortality risk and life expectancy (Aichele, Rabbitt, & Ghisletta, 2015; Gottfredson & Deary, 2004; Neisser et al., 1996). Additionally, this construct is associated with brain reserve, which is the individual's brain capacity to tolerate insults and pathological processes without showing clinical deficits or symptoms (Schmand, Smit, Geerlings, & Lindeboom, 1997).

Strong evidence points to event-related potential (ERP) components as physiological correlates of Gf (Amin, Malik, Kamel, Chooi, & Hussain, 2015; Bazana & Stelmack, 2002; Beauchamp & Stelmack, 2006; De Pascalis, Varriale, & Matteoli, 2008; Duan, Shi, Sun, Zhang, & Wu, 2009; Jaušovec & Jaušovec, 2001; Schlottfeldt, Mansur-Alves, Flores-Mendoza, & Tierra-Criollo, 2018; Wronka, Kaiser, & Coenen, 2013; Zhang et al., 2007; Zhang, Shi, Luo, Zhao, & Yang, 2006). Among them, P300 (or P3) has been particularly related to Gf (Amin et al., 2015; Jaušovec & Jaušovec, 2001). It is a positive wave peaking around 350 and 600 ms (Luck, 2012). It is related to the "context updating", meaning for the adjustment of attentional resources called when a revision of the representation of the current environment is required (Donchin, 1981). More specifically, P300 amplitude is related to the investment of attentional resources during the performance of a task (Luck, 2005), while its latency is sensitive to the time needed for stimulus detection and rating (Polich, 2007). P300 may comprise several subcomponents. For instance, there is a wide consensus in the distinction between a subcomponent with maximal amplitude in the frontal electrodes, named P3a, and another subcomponent that peaks at parietal sites, known as P3b (Polich, 2007). P3b component is the most traditional subcomponent and so it is normally called by P300 in most studies (Dinteren, Arns, Jongsma, & Kessels, 2014).

Another component that has been related with Gf is a late positive wave with a centro-posterior maximum, occurring around 500 and 800 ms, which has been called "Late Positive Complex" (LPC) or

also "Positive Slow Wave" (Gevins & Smith, 2000). Although, there is an ongoing debate regarding the cognitive mechanisms involved in this component generation, it seems to be related to recognition memory, categorical response, memory match, decision accuracy, and maintenance of a visual working memory representations (Danker et al., 2008; Gunseli, Meeter, & Olivers, 2014; Schendan & Maher, 2009). P200 (or P2) is a third component which is also considered in Gf studies (Burns, Nettelbeck, & Cooper, 2000; Jaušovec & Jaušovec, 2001; Riccio, Reynolds, Lowe, & Moore, 2002). It is a positive waveform with an anterior and central maximum distribution peaking between 100 and 250 ms after stimulus presentation (Crowley & Colrain, 2004). It is related to stimulus evaluation and context updating, and it has been advanced as an initial stimulus pre-classification prior to the P300 (Crowley & Colrain, 2004; Lenartowicz, Escobedo-Quiroz, & Cohen, 2010).

Age-related changes in these ERP components have been reported in the literature. For example, P300 was found to be attenuated and delayed in health older people (Dinteren et al., 2014; Falkenstein, Gajewski, & Getzmann, 2014; Lubitz, Niedeggen, & Feser, 2017; Schapkin, Gajewski, & Freude, 2014) and abnormalities in this component were observed in mild cognitive impairment and pathological aging (Gu et al., 2018; Lai, Lin, Liou, & Liu, 2010; Olichney et al., 2008; Olichney et al., 2002; Waninger et al., 2018; Zurrón et al., 2018). LPC differences were observed when comparing older with younger adults (Getzmann, Hanenberg, Lewald, Falkenstein, & Wascher, 2015; Wolk et al., 2009), and healthy older adult and those with cognitive impairment (Waninger et al., 2018) or dementia (Lubitz et al., 2017). Similarly, P200 has been distinguishing younger and older adults (Bourisly & Shuaib, 2018; Lubitz et al., 2017; Schapkin et al., 2014; Wolk et al., 2009), as well as healthy and pathological aging (Waninger et al., 2018).

Previous studies have related the P300 and LPC amplitude and latency with Gf in young adults (Amin et al., 2015; Beauchamp & Stelmack, 2006; Dichter, Van Der Stelt, Boch, & Belger, 2006; Gevins & Smith, 2000; Jaušovec & Jaušovec, 2000; McGarry-Roberts, Stelmack, & Campbell, 1992; Polich, 2007; Wronka et al., 2013) and children (Duan, Shi, & Wu, 2009; Schlottfeldt et al., 2018). In general, these studies have shown that Gf high-performance (HP) individuals present larger P300 and LPC amplitude and shorter P300 latency compared to low-performance (LP) individuals, except for one study that showed a contradictory result in which HP participants exhibited a longer P300 latency than LP participants (Houlihan, Stelmack, & Campbell, 1998). Regarding P200, some studies did not observe differences in the P200 component when comparing HP and LP young adults in Gf tasks (Amin et al.,

2015; Duan, Shi, & Wu, 2009); in contrast, other studies have reported an association between the P200 latency and Gf in participants aging between 18 and 75 years old (Schubert, Hagemann, Voss, Schankin, & Bergmann, 2015) or in a sample of young adults alone (Burns et al., 2000). In fact, evidence on the relationship between the P200 and Gf is scarce, mixed and mainly circumscribed to young adults.

Exploration of the association between ERPs and Gf in the elderly is relevant as it may allow the identification of neurophysiological correlates of successful aging, given that Gf is a central process in the functioning of the older people (Aichele et al., 2015; Gross, Rebok, Unverzagt, Willis, & Brandt, 2011; Oliveira et al., 2012). For the best of our knowledge, no study has been yet performed assessing the association between the P200, P300 or LPC components (amplitude and latency) with Gf in older people. Therefore, the aim of this study was to assess P200, P300 and LPC latency and amplitude during the execution of an oddball paradigm and an identical pairs-continuous performance task (CPT) as potential markers of Gf. For that end, we contrasted the P200, P300 and LPC amplitude and latency among HP and LP individuals, split by the median of Raven's Advanced Progressive Matrices (RAPM) performance. Our hypothesis was that the HP group would present higher P300 and LPC amplitude and shorter P300 latency when compared to the LP group, while no P200 differences were expected, according to previous studies (see Amin et al., 2015; Gevins & Smith, 2000). Finally, we tested the predictive relationship between ERPs and Gf by assessing the correlation between the ERP amplitude and latencies and the RAPM scores, as well as, by applying a regression analysis and a receiver operating characteristic (ROC) curve.

Method

Participants

Fifty-seven community-dwelling older people (42 females; mean age: 68.19 ± 5.78 years old) were recruited from senior daycare centers and in sport and recreation clubs in the North of Portugal. See Table 1 for sample characteristics. All participants were right-handed, as assessed by the Edinburgh handedness inventory (Oldfield, 1971). They were healthy, had normal or corrected-to-normal visual (≥20/40 in both eyes) and auditory acuity, as well as no history of neurological or psychiatric disorders. All included participants scored above Montreal Cognitive Assessment (MoCa) cut off (of 2 standard deviation) for cognitive impairment following the normative score of the Portuguese population,

according to age and educational level (Freitas et al., 2011). Participants were excluded if they scored 10 or more points in Geriatric Depression Scale (Pocinho, Farate, Dias, Lee, & Yesavage, 2009). The study was performed in accordance with the Declaration of Helsinki and approval was obtained from the ethics subcommittee for Life and Health Sciences of University of Minho (SECVS 012/2016). Participants gave informed consent before their inclusion in the study.

Table 1

Sample Demographic Characteristics

Demographic characteristic	LP group (n = 28)		HP group (n = 29)	
	M/ Frequency	*SD*	*M*/Frequency	*SD*
Age (years)	69.64*	5.53	66.79*	5.77
Education (years)	6.29	3.93	8.90	5.91
Gender (Male/Female)	7/21	–	8/21	–

Note. *Indicates presence of statistical difference between groups verified by Mann-Whitney test (age and years of formal education) and chi-square (gender), $p < .05$. Abbreviations. *M* = Mean; HP = High-performance; LP = Low-performance; *SD* = Standard Deviation.

Gf Task

The RAPM (Raven, Raven, & Court, 1998) (set 1 and 2) was applied outside the EEG session. The RAPM (Raven et al., 1998) is widely used as a standardized Gf measure due to its high loading in g factor as revealed by factorial analyses studies and high sensitivity to individual differences (Gray & Thompson, 2004; Jensen, 1998; Unsworth, Heitz, & Engle, 2005). RAPM has been the outcome selected for assessing the effectiveness of many trials on cognitive training (Cantarella, Borella, Carretti, Kliegel, & De Beni, 2017; Heinzel et al., 2016, 2013; von Bastian & Oberauer, 2013; Xin, Lai, Li, & Maes, 2014; Zinke, Zeintl, Eschen, Herzog, & Kliegel, 2011). The RAPM consists in the visual presentation of 48 images, each one organized in a 3x3 matrix of lines and geometric shapes, wherein one of the shapes is missing. Participants were asked to select from eight options the shape that completed the matrix. A score of 1 for correct responses or 0 for errors was assigned for each item. In this experiment, only 24 items were applied (the even or odd items) with no time restriction for participants' response.

ERP tasks

The typical task used to elicit the P300 is the traditional oddball paradigm. In an active visual oddball task, two different figures are shown to the participant, one is marked as the target and is less frequently presented (deviant stimulus) than the other figure (standard stimulus), which is considered the non-target. Participants' task is to respond (i.e., mentally counting or pressing a button) whenever they are presented with the target stimulus. In the current study, the visual oddball task (see Figure 1A) comprised 150 trials, in which participants were randomly presented with a white circle or star on the center of a black screen (visual angle of 3.26 ° x 3.26°, both figures). Figures remained visible for 750 ms and were separated by a jittered interval between 1250-1450 ms. The circle was presented in 80% of the trials (standard stimulus), while the star appeared in 20% of the trials (deviant target stimulus). Participants were instructed to silently count the number of stars displayed on the screen and say the total at the end of the task. The task lasted approximately six minutes.

The CPT is another attentional task that elicits the LPC and is highly sensitive to brain dysfunction (Cornblatt, Lenzenweger, & Erlenmeyer-Kimling, 1989; Riccio et al., 2002). In this task, individuals are presented with a sequence of visual stimuli, one at a time, and they must respond when a target stimulus is presented. A version of this task is the identical pairs-CPT (Cornblatt et al., 1989; Crego et al., 2010), in which a target is the consecutive repetition of any item in a sequence. Identical pair-CPT is considered to be a more complex task compared to the oddball paradigm as it depends on more controlled processing (Riccio et al., 2002; Shucard, McCabe, & Szymanski, 2008). In the current study, during the CPT task (see Figure 1B), participants had to decide whether the stimulus presented was the same as the one presented immediately before in a sequence (match) or not (non-match). So, they were instructed to press the key 6 (marked with a green check symbol) in a numeric keypad (CHERRY G84-4700 Keypad) for a match stimulus, and key 4 (marked with a red 'X') for a non-match. The task lasted approximately 13 minutes, including 200 trials, in which 60 different white geometrical figures (size 4.0 ◦ x 4.0 ◦ visual angle) were presented for 2000 ms in the center of a black screen and separated by an inter-stimulus interval ranging from 1500 to 1800 ms. In addition, the presentation of the stimuli was pseudo-randomized, so the proportion target and non-target trials was 1:4.

For both tasks, a fixation cross was presented in the center of the screen whenever there were no visible stimuli on screen in order to reduce ocular artifacts. Before both tasks, participants received a

brief training to confirm that they understood the instructions. The order of the tasks was counterbalanced across participants.

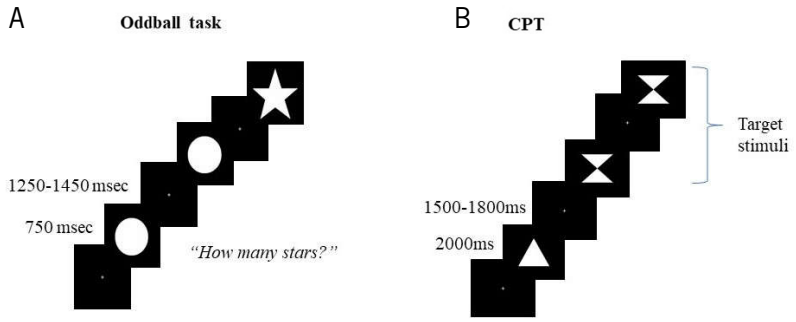

Figure 1. Schematic illustration of the EEG tasks. *Note.* (A) Oddball task. (B) Identical Pairs-Continuous Performance Task (CPT).

Procedure

The RAPM were performed in the day before the EEG data collection. During EEG recording, inside an electrically shielded, soundproof room with dimmed light, participants were comfortably seated in an armchair in front of a monitor (LG ACPI x86) placed 100 cm in front of their eyes. Presentation software package (version 18.3; Neurobehavioral Systems, Albany, CA) was used to display data and record the responses.

EEG data acquisition and analysis

Continuous EEG data band-pass filtered between 0.01 and 100 Hz were digitally recorded through a 64-channel Biosemi ActiveTwo system (Biosemi, Amsterdam, The Netherlands) at a sampling rate of 512Hz for offline analysis. The 64 active Ag/AgCl scalp electrodes were arranged according to the international standard 10–10 system for electrode placement (Chatrian et al., 1985), using a nylon head cap. Five additional active electrodes were placed in the lateral canthi of both eyes (horizontal electrooculograph - HEOG), bellow left eye (verticta electrooculograph - VEOG) and in right and left mastoids. As per BioSemi system design, all electrodes were referenced to the common mode sense (CMS) active electrode and grounded to a passive electrode. Further, active electrode offset was maintained below 25 mV.

EEG analysis was performed using EEGLAB (version 14.1.1) (Delorme & Makeig, 2004) and ERPlab plugin (version v6.1.4)(Lopez-Calderon & Luck, 2014), run in Matlab package (version 2016a). Data were passed through a digital phase-shift free Butterworth filter with the high cut-off frequency at half power (-3dB) set at 30 Hz (12 dB/octave roll-off) and a low cut-off frequency at half power set at 0.1 Hz (12dB/octave roll-off). DC-bias was removed. Artifacts were rejected after visual screening for anomalies. Interpolation of visually identified noisy channels (M = 1.14 channels/participant; SD = 1.18) were done by using spherical interpolation, with a maximum of four interpolated channels. Data were referenced offline to the average of the left and right mastoids. An independent component analysis (ICA) (Jung et al., 2001) of the data allowed the identification and deletion of components with clear ocular, muscular or noisy activity. Data were segmented in epochs from -100 ms before stimulus presentation to 900 ms post-stimulus. Baseline was corrected with the mean activity in the 100 ms prior to sample stimulus. Artifact rejection was applied on the epoched data by using ERPLAB's functions: simple voltage threshold and sample to sample voltage threshold. Epochs were marked for rejection when the voltage were less than -150 μV or greater than 150 μV or when the difference between consecutive samples was superior to 50 μV.

Five participants were excluded of the CPT analysis: four had more than 25% of trials rejected during artifact rejection, and one participant did not understand the task and was not able to perform it accurately. No participant was excluded from the oddball analysis. Conditions did not differ in the number of non-rejected epochs and percentage of rejected epochs ($p > .05$).

Five averaged ERP waveforms were extracted for each subject: standard stimulus, deviant stimulus, and deviant-standard difference waveforms considering the oddball paradigm; Match and Non-match for the CPT. For the oddball task, the P200 (for standard and deviant waveforms) and P300 (for the difference wave) were analyzed. For the CPT, the P200 and LPC were considered separately for the conditions (match/non-match). In all cases, the P300 and LPC amplitude and latency were calculated from six centro-parietal electrodes (P3, Pz, P4, CP3, CPz and CP4), while the P200 amplitude and latency were calculated from frontal and fronto-central electrodes (F3, Fz, F4, FC3, FCz, and FC4). Statistical analyses were performed on the mean values of the electrodes, at which each component was measured (see Figure 2*Figure*). Grand averages in Fz, Cz and Pz were calculated for each group for visualization purposes only.

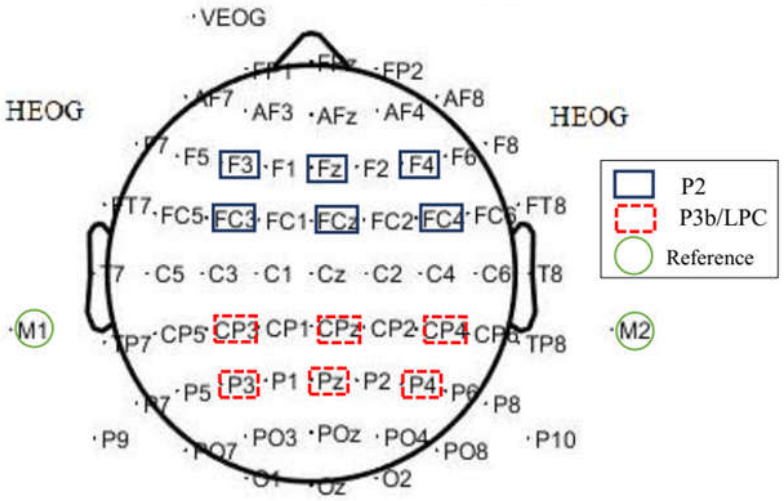

Figure 2. Electrode positions. *Note.* Solid blue rectangle represents electrodes used to measure P200 component amplitude and latency. Dashed red rectangles mark electrodes used to measure P300 and LPC components amplitude and latency. Green circles signal reference electrodes.

Time windows for mean amplitude calculation were selected according to visual inspection and equally distributed around the peak latency. For the oddball task, the time windows for P300 were 382-582 ms, and for P200 were 149-219 ms. For the CPT, 350-800 ms for the LPC, and 170-240 ms for the P200. In this task, only epochs corresponding to correct responses occurring between 200 and 3500 ms after the onset of a matching stimulus entered the analysis.

Statistical data analyses

Statistical analyses were performed on the Statistical Package for the Social Sciences (SPSS) Version 24.0 (SPSS Inc., Chicago, IL, USA), adopting an alpha level of .05. Only significant results were reported (for overall results, see Supplementary Material, Table S1). Effect sizes were calculated through Cohen's d (*d*). Participants were divided in HP, if they performed equal or above the median of raw scores in RAPM (set II) (*Md* = 4), and LP, if their performance was below the median.

First, we verified group differences in the raw scores of the RAPM. Then, the behavioral analysis of EEG tasks was performed only for the CPT task, as in the oddball task the participants output was restricted to the total number of stars counted during the task. The outcomes considered were reaction time (RT) from stimulus onset to button press (considered only for correct responses) and accuracy (D-prime) (Hautus, 1995; Stanislaw & Todorov, 1999). Student's *t*-tests for unpaired groups were

performed comparing HP with LP groups behavioral outcomes as well as the mean amplitude and local peak latency for each ERP component. When normality was not verified, the Mann–Whitney U-test was used. We also confirmed between-group results with Bayesian analysis (see supplementary material, Table S2) run in Jasp software, version 0.9.2 (JASP Team, 2018).

Additionally, bivariate correlation analyses were performed to test the association between the ERPs that were significant in between-group analysis (LPC/match mean amplitude; LPC/non-match mean amplitude; P300 peak latency) and RAPM measures (Table 2). When both variables in the analysis were normally distributed, we used Pearson's correlation coefficient, otherwise Spearman's correlation coefficient was performed. An additional multiple linear regression analysis was conducted to assess if those ERP components could predict Gf. Assumptions for linear regression were checked and stepwise method was performed with the ERP components as predictors, and RAPM scores in set 2 as dependent variable. There was one outlier in the total sample regarding RAPM scores, however a sensitive analysis indicated no change in the results when this participant was excluded. Therefore, we considered data derived from this participant in the analysis. Finally, we used the ROC curves to assess the predictive discrimination of ERP components to identify HP and LP individuals in Gf (Pencina, D'Agostino, D'Agostino, & Vasan, 2008).

Results

Behavioral data

The RAPM average for the LP group (M = 2.00, SD = 1.12) was significantly lower than the HP group RAPM average (M = 5.00, SD = 1.79; U = 0,00, p < .01). No significant differences between the HP and LP groups were observed for response time (RT) (t(50) = 1.29, p > .05, d = 0.36, 95%CI [-25.64, 118.58]) or accuracy (t(50) = - 1.61, p > .05, d = 0.03, 95%CI [- 0.60, 0.07]) in CPT (see Table 2 and Figure 3).

Table 2

Behavioral Data for HP and LP in CPT task

Behavioral performance	HP (n = 29)	LP (n = 28)
Correct response time (ms)	796.60 (118.40)	845.07 (142.13)
D-prime	3.78 (0.54)	3.51 (0.67)

Note. Data are presented as mean (standard deviation). *Indicates presence of significant statistical difference between groups verified by independent-samples T test, $p < .05$. Abbreviations. HP = High-performance; LP = Low-performance.

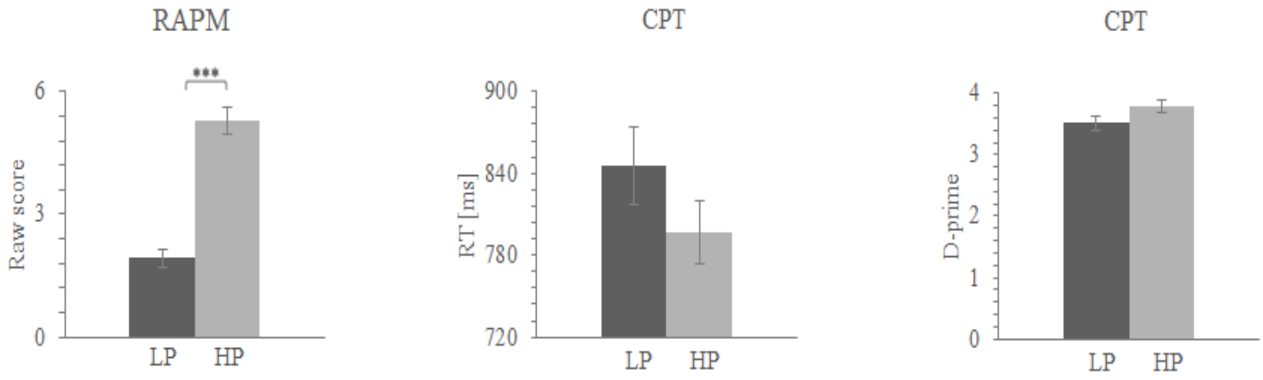

Figure 3 Raw mean scores in the RAPM and mean RT and D-prime for the CPT for each group*. Note.* Error bars represent standard errors. ^$p < .1$, *p < .05, **$p < .01$, ***$p < .001$. Abbreviations. RAPM= Raven's Advanced Progressive Matrices, CPT= continuous performance task, LP = low-performance; HP = high-performance; RT = response time.

Electrophysiological data

See Figure 4 for HP and LP groups grand-average ERPs elicited by standard and deviant stimuli in the oddball task as well as the deviant-standard difference waveform; match/non-match stimuli in the CPT.

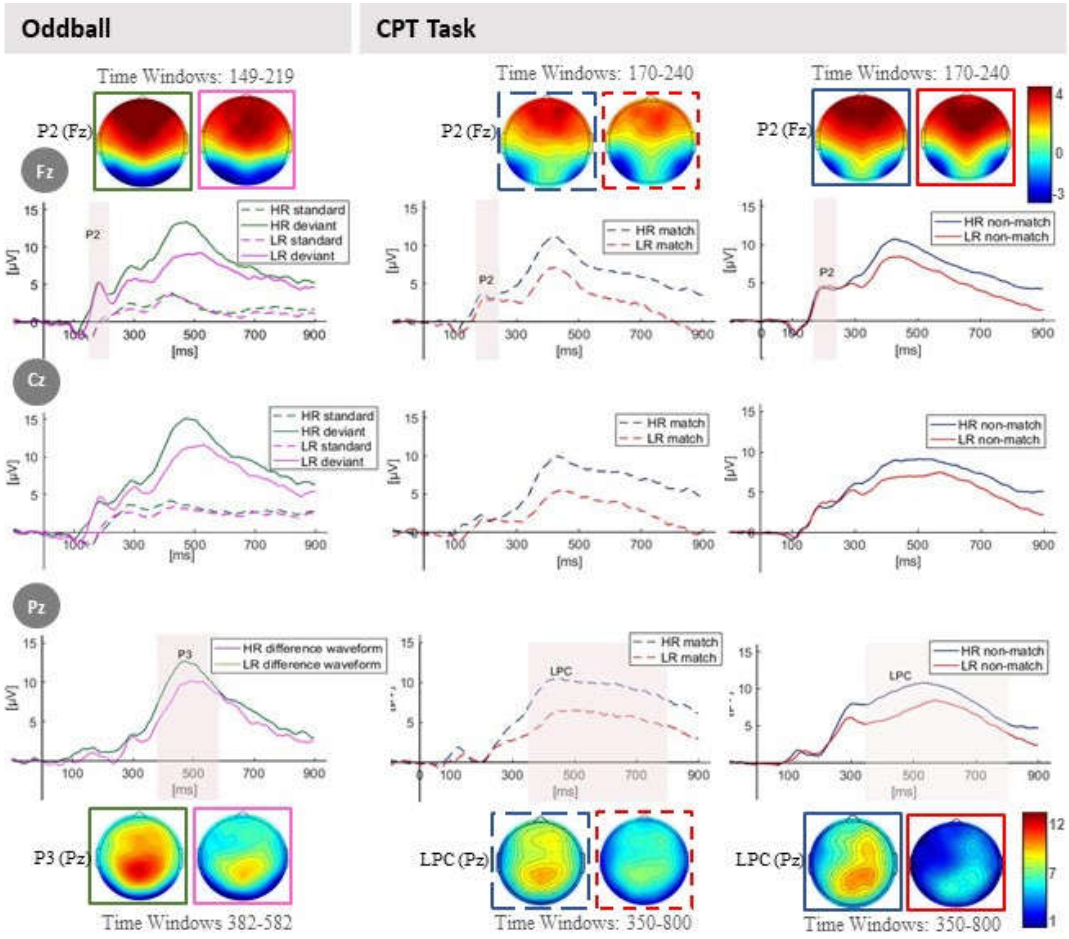

Figure 4. ERP waveforms (FZ, Cz and Pz electrodes) comparing LP and HP groups during CPT and Oddball performance. Topographic plot of the ERP waveforms for both tasks in Fz (Top) and Pz (Bottom).

Group differences in oddball

P200

No significant differences ($p > .05$) were observed between HP and LP groups in P200 amplitude or latency for both standard and deviant conditions.

P300

No group differences were observed for P300 amplitude ($p > .05$), while P300 latency was shorter for the HP ($M = 473.92$, $SD = 39.41$) than the LP group ($M = 503.24$, $SD = 40.71$; $t(55) = -2.76$, $p = .008$, $d = -0.73$, 95%CI [-50.58, - 8.05]; $BF_{10} = 5.80$).

Group differences in match and non-match conditions of the CPT

P200

No significant effects were found for P200 amplitude and latency elicited by match or non-match stimuli ($p > .05$) in the CPT.

LPC

For match stimuli, LPC mean amplitude was higher for the HP group ($M = 8.56$, $SD = 4.36$) in comparison with the LP group ($M = 4.92$, $SD = 3.65$; $t(50) = 3.26$, $p < .001$, $d = 0.91$, 95%CI [1.40, 5.88]; $BF_{10} = 17.58$). No significant group differences were observed for local peak latency ($p > .05$).

For non-match stimuli, the LPC amplitude was larger in the HP group ($M = 8.13$, $SD = 3.37$) than the LP group ($M = 6.13$, $SD = 3.59$) ($t(50) = 2.07$, $p = .04$, $d = 0.57$, 95%CI [0.06, - 3.94]). However, Bayesian analysis did not support these results ($BF_{10} = 1.57$), suggesting no group differences in amplitude for non-match stimuli. No significant group differences were observed for LPC local peak latency ($p > .05$).

Figure 5 shows the observed group differences. The results did not alter when we performed an Analysis of covariance (ANCOVA) controlling for age or age and education. Additionally, Bayesian analysis confirmed no group differences in those variables ($BF_{age} = 1.188$; $BF_{education} = 1.29$).

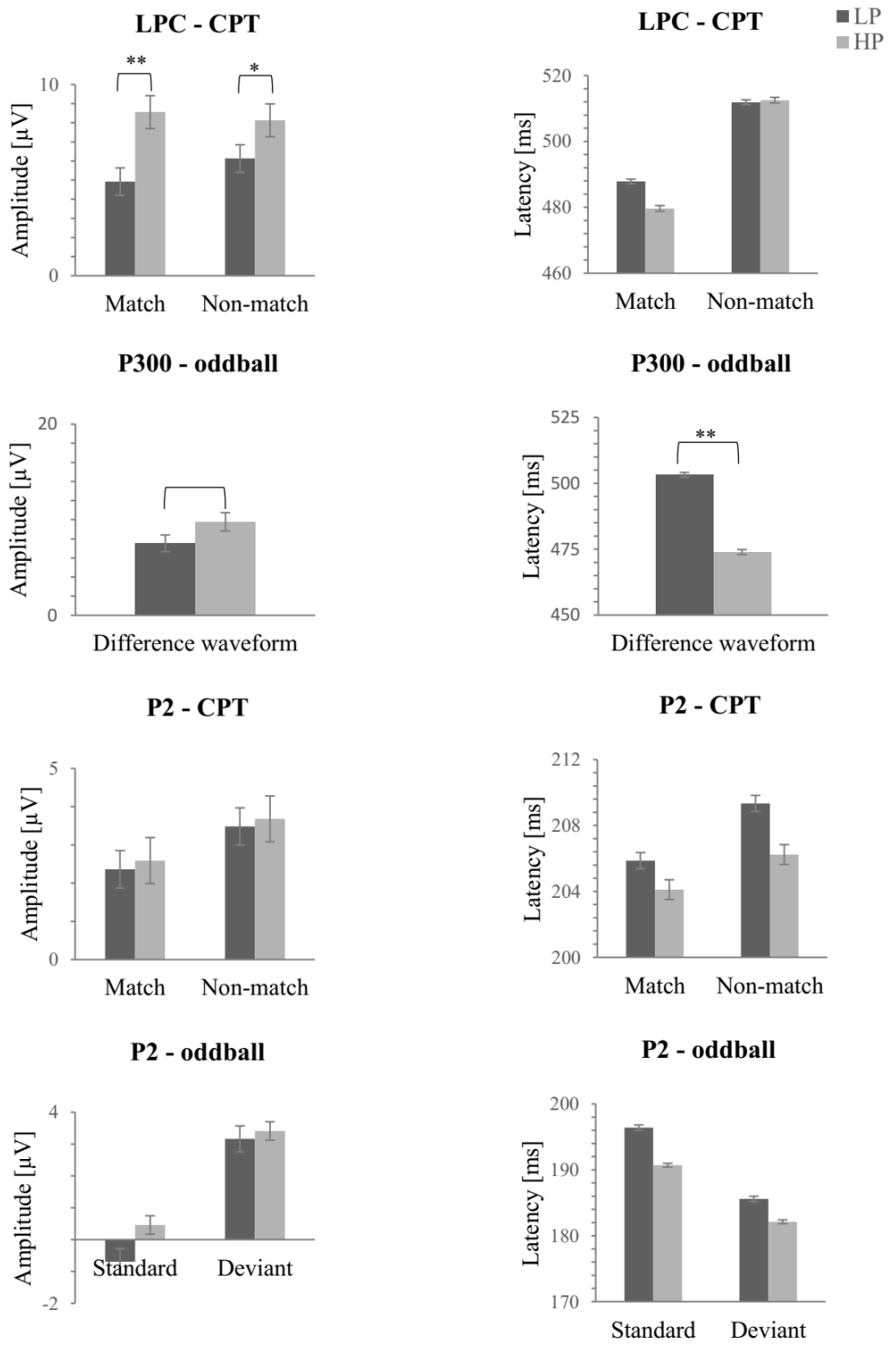

Figure 5. Bar graph representing LPC, P300 and P200 amplitudes and local peak latencies for match/non-match and standard/deviant conditions, as well as deviant-standard difference waveform. Error bars represent the standard error $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$

Predictive analysis

Small statistically significant correlation coefficients were identified for D-prime, P300 latency, LPC/match amplitude and LPC non-match amplitude with RAPM (set II) scores (see Table 3).

Table 3

Correlations Between ERPs, D-prime and RAPM scores

Outcomes	D-prime	RAPM (set II)	P300 lat	LPC match amp	LPC non-match amp
D-prime	1	0.280*[1]	-0.241	0.104	0.113
RAPM (set II)	0.280*[1]	1	-0.321*[1]	0.417**[1]	0.303*[1]
P300 lat	-0.241	-0.321*[1]	1	-0.39**	-0.242
LPC match amp	0.104	0.417**[1]	-0.39**	1	0.766**
LPC non-match amp	0.113	0.303*[1]	-0.242	0.766**	1

Note. Lat = latency. Amp = Amplitude; [1]Spearman correlations. ^$p < .1$, *$p < .05$, **$p < .01$, ***$p < .001$.

A multiple linear regression was performed to predict RAPM (set II) score based on LPC/match amplitude, LPC/non-match amplitude, and P300 latency. Stepwise method excluded two variables from the analysis (LPC amplitude for non-match stimuli and P300 latency), so only LPC/match was entered as predictor in the model. The model achieved statistical significance ($F(1, 50) = 5.75$, $p < .05$, with an $R^2 = 0.103$). Predicted RAPM score is equal to the equation 2.55+0.17*(LPC/match amplitude). A bootstrapping procedure with 1000 replications (resampling with replacement), bias-corrected coefficients and confidence intervals was used to validate the model. Thus, LPC/match amplitude was observed to be a significant predictor of RAPM score. The predicted RAPM score derived from the regression analysis was compared with the RAPM group state (HP versus LP) in a ROC curve. The results showed an AUC (area under the curve) of 0.75, 95%CI [0.62, 0.89] (Fan, Upadhye, & Worster, 2006), showing a moderate discriminative power of LPC/match amplitude.

Discussion

In this work we assessed if the late endogenous ERP components - P2, P300 and LPC - could works as putative markers of Gf in healthy older adults. For such, we have investigated P200, P300 and LPC differences between LP and HP older individuals and assessed the predictive relationship between ERPs and RAPM scores. In general, between-group difference, correlation, linear regression and ROC curve analyses supported the ERPs as a marker of Gf.

Gf is a cognitive construct that has always drawn much attention, especially because of its closer relationship with important life achievements, such as health in later life, mortality, daily decision-making, professional success, occupational attainment, social mobility, and school performance (Deary, Penke, & Johnson, 2010). Besides extensive cognitive, adaptive and functional characterization of the Gf, this construct has also been studied with EEG techniques. In accordance, the literature is abundant in showing the relationship between the Gf and specific EEG signal indices. Mostly, these studies investigated the difference in late endogenous components, specifically when comparing LP and HP individuals. They showed that HP individuals are faster, with shorter ERP latencies. Also, HP participants have more capacity of processing information, as shown by their higher level of accuracy and larger amplitudes of late endogenous components in comparison to LP individuals (Burns et al., 2000; Gevins & Smith, 2000; Jaušovec & Jaušovec, 2001). However, these studies were only performed with young adults (Amin et al., 2015; Bazana & Stelmack, 2002; Beauchamp & Stelmack, 2006; De Pascalis et al., 2008; Jaušovec & Jaušovec, 2001; Wronka et al., 2013) or children (Duan, Shi, Sun, et al., 2009; Schlottfeldt et al., 2018; Zhang et al., 2007, 2006). The current study extends this evidence to the older population.

Not surprising, we observed that the RAPM scores were significantly different between HP and LP groups, documenting different levels of Gf performance. Furthermore, behavioral findings of CPT suggested that HP participants had a higher accuracy and shorter RT in CPT compared to LP, but it was not statistically significant. Shorter RT is expected in HP group since the literature presents solid evidence of the negative relationship between processing speed and Gf (e.g., Salthouse, 1991; Schretlen et al., 2000). It is likely that CPT is not a difficult enough task nor a task demanding a substantial cognitive processing. So, both groups had a high performance in the task (d-prime>3), with low variability observed, which could indicate a ceiling effect for performance.

Regarding the group differences (LP vs. HP) in EEG data, electrophysiological brain activity significantly differed between groups. In particular, LPC amplitudes for match-stimuli were statistically higher and P300 latency was statiscally shorter in the HP group in comparison with the LP group. Analysis of P300 amplitude did not achieve significance (p = .09) nor was substantial evidence using Bayesian Methods. The difference in amplitude was more robust in LPC probably because it was elicited by the CPT task, which is more cognitively demanding than the oddball paradigm (O'Reilly, Braver, & Cohen, 1999). In the LPC, participants compare each stimulus with the previous one. Thus, in each

stimulus, the participants must actively update the target, whereas in the oddball paradigm the participants only need to respond to the same target stimuli.

LPC has been associated to working memory maintenance processes, categorization or encoding of information (Chen et al., 2007; Duan, Shi, Sun, et al., 2009; Folstein & Van Petten, 2011; García-Larrea & Cézanne-Bert, 1998). Therefore, limitation in working memory processing may be a factor underlining the low performance of some individuals in Gf tests. Indeed, a set of evidence showed that working memory is a determinant factor of Gf (Heitz, Unsworth, & Engle, 2005).

As previously mentioned, another factor that may be linked to low Gf performance is the slowing of processing speed (Salthouse, 1991; Schretlen et al., 2000). P300 peak latency might be related to the time expended to categorize a stimulus and thus could work as an index of processing speed (Folstein & Van Petten, 2011). Aging is associated with neural density and myelination losses, as well as with a reduction in neurotransmitters (Heitz et al., 2005). Consequently, a decreasing in processing speed accompanies the aging process, and it is supposed to be at the core of age-related cognitive decline (Salthouse, 1996; Schretlen et al., 2000). In this regard, one could infer that LP individuals present a more marked slowing of processing speed as suggested by the higher ERP latencies compared to HP participants. In fact, LP group had a delayed peak latency in P300 in relation to HP group. However, in our study, difference on latency was found only for the P300 elicited by the oddball task. There was no difference in LPC latency elicited by the CPT. In line with our study, Gevins and Smith (2000) found significant difference in LPC amplitude elicited by a 1-back comparing high, medium, and low performance, whereas no difference in latency was observed. The lack of difference in LPC latency between LP and HP groups may be due to the inter-individual variation on the LPC waveforms (Kos, van den Brink, & Hagoort, 2012).

In the current study, P200 did not differ between groups. This finding is in accordance with previous literature (Amin et al., 2015; Duan, Shi, & Wu, 2009). P200 is related to the evaluation of task relevant features (Potts, 2004). Similar to P300, P200 amplitude increases when the target is relatively infrequent. However, unlike the P300, the P200 amplitude also varies with very simple manipulations of the perceptual features of the target stimulus (e.g., stimulus color) (Luck, 2005). Superior cognitive performance is thought to be more associated with P300 (Polich, 2007), which might explain why the groups differed only in later components. P200 component may be less associated with the efficiency on high-complex cognitive processes, such as those required during RAPM performance.

Our findings are also in agreement with studies with clinical population, as they showed late endogenous ERP components as a putative biomarker for general cognitive abilities (Pavarini et al., 2018; Polich, 2007). For instance, these components latencies were find to be delayed in mild cognitive impairment and dementia compared to their healthy peers, while LPC amplitude was shown to be decreased in both populations (Olichney et al., 2006) and P300 in patients with dementia (Egerházi, Glaub, Balla, Berecz, & Degrell, 2008). Lai et al. (2010) suggested that P300 latency is a more sensitive tool to follow Alzheimer patients progression in comparison to neuropsychological tests.

Accuracy in CPT was correlated with RAPM scores, which indicates a relationship between the task used in the EEG with Gf. Likewise, correlation analysis yielded a statistically significant positive correlation between ERP amplitudes and RAPM scores, as well as, a negative weak correlation between P300 latency and RAPM scores. These results are in line with Gevins and Smith (2000), which similarly found a correlation between amplitude of LPC elicited by a 1-back task and WAIS-R scores. In comparison with Gevins and Smith´s study, we failed to find a correlation between ERP and CPT accuracy, probably because CPT was an easy task for most participants and ceiling effect was observed in participants' behavioral performance.

Lastly, LPC amplitude of match stimuli significantly predicted RAPM scores, confirming its relationship with the Gf. The addition of the other two predictors (amplitude of non-match stimuli and P300 latency) did not improve the model. This suggest that LPC amplitude to match stimuli account for most of the variance, being better predictor than the other two variables. Similarly, the Bayesian Analysis of the current study did not confirm group differences in LPC elicited by the non-match stimuli, whereas the Bayes Factor of LPC amplitude for match stimuli was much bigger than the Bayes Factor of P300 latency. Therefore, LPC amplitude for match stimuli seems to constitute a better marker compared to the other ERP components. The validity of LPC amplitude to match stimuli as marker of RAPM score was also confirmed by ROC curve, which demonstrated the predictive capacity of LPC amplitude for discrimination between LP and HP individuals in Gf.

In this study, we observed that LP participants displayed a decreased amplitude and an increased latency in comparison to HP individuals in LPC and P3b respectively. The same pattern was observed in studies comparing young and older adults, in which the amplitude was decreased and the latency was delayed throughout life-span (Emmerson, Dustman, Shearer, & Turner, 1989; McEvoy, Pellouchoud, Smith, & Gevins, 2001; Pinal, Zurrón, & Díaz, 2015; Polich, 2007; Saliasi, Geerligs, Lorist,

& Maurits, 2013). It could be postulated that more cognitively efficient elders might present a more young-like electrophysiological pattern. Therefore, future studies should address this hypothesis, contrasting HP individuals´ performance with those of younger adults.

Additionally, in order to strength the evidence in favor of the late endogenous components as a complementary tool in the assessment and screening of elderly people (Pavarini et al., 2018), futures studies could assess if such ERPs work as an index for more functional outcomes (Ribeiro et al., 2018). These studies could contribute for the development of a metric of ERPs to assess the impact of intervention protocols, such as cognitive training (Du, Ji, Chen, Tang, & Han, 2018; Gajewski & Falkenstein, 2018; Pergher, Wittevrongel, Tournoy, Schoenmakers, & Van Hulle, 2018). Additionally, other markers for Gf, such as genetic metric, could be identified in the elderly population (Deary et al., 2010).

One limitation of this study was the sample size, which may be unpowered to identify differences in behavioral analysis of CPT and possibly in EEG analysis of P300 amplitude. However, we addressed this issue by running a complementary Bayesian Analyses in the data to confirm our findings. The dichotomization of the RAPM score in a median split could be also a limitation, since it may lead to loss of information, variability and power (MacCallum, Zhang, Preacher, & Rucker, 2002). However, we overcome this limitation by performing a correlation and a regression analysis to corroborate our findings.

The understanding of the neurophysiological determinants of the Gf shed light on the neural mechanisms behind this construct, which is important for the development of markers in the field. Especially in the elderly, whose aging-related changes in brain function may arise latently in a neural process-level prior to behavioral manifestation (Zöllig & Eschen, 2009). Therefore, ERPs could be very informative of cognitive processing and could be used in complement to cognitive and neuropsychological assessment of older people, allowing early intervention when it is needed (Falkenstein, Gajewski, & Getzmann, 2014). In fact, our findings highlighted the role of ERP components, in particular the LPC amplitude, as an electrophysiological proxy of Gf abilities in the elderly, extending prior evidence by probing such relationships already observed in young adults in healthy older adults.

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Appendix D

Supplementary material (study V)

Table S1

Results of t-test Analysis of Group Difference (LP versus HP) in Amplitude (amp) and Latency (lat)

	Component	Condition	Amp/ lat	Mean (SD) LP	Mean (SD) HP	*t* test results	p-value	Cohen's d	95% CI
CPT	LPC	Match	Amplitude	4.92 (3.65)	8.56 (4.36)	*t*(50)=3.26	**<0.01**	0.91	[1.40, 5.88]
	LPC	Match	Latency	487.84 (64.66)	479.67 (59.95)	*t*(50)=-0.47	0.64	-0.13	[-42.91, 26.56]
	LPC	Non-match	Amplitude	6.13 (3.59)	8.13 (3.37)	*t*(50)=2.07	**0.04**	0.57	[0.06, 3.94]
	LPC	Non-match	Latency	511.92 (72.27)	512.53 (59.48)	*t*(50)=0.03	0.973	<0.01	[-36.29, 37.51]
	P2	Match	Amplitude	2.33 (2.57)	2.95 (3.12)	*t*(50)=0.78	0.441	0.22	[-0.98, 2.21,]
	P2	Match	Latency	205.01 (17.09)	204.75 (17.80)	*t*(50)=-0.06	0.956	-0.02	[-9.99, 9.45,]
	P2	Non-match	Amplitude	3.45 (2.85)	4.03 (2.81)	*t*(50)=0.74	0.46	0.21	[-1.00, 2.16]
	P2	Non-match	Latency	209.38 (16.95)	206.43 (18.11)	*t*(50)=-0.61	0.55	-0.17	[-12.72, 6.82]
Oddball	P3	Wave difference	Amplitude	7.54 (4.60)	9.78 (5.17)	*t*(55)=1.73	0.09	0.46	[-0.36, 4.84]
	P3	Wave difference	Latency	503.24 (40.71)	473.92 (39.41)	*t*(55)=-2.76	**0.008**	-0.73	[-50.58, -8.05]
	P2	Standard	Amplitude	-0.693 (2.18)	0.459 (1.54)	*t*(55)=0.47	0.640	0.13	[-0.76, 1.23]
	P2	Standard	Latency	196.40 (13.88)	190.70 (11.92)	*t*(55)=-1.67	0.102	-0.48	[-12.56, 1.16]
	P2	Deviant	Amplitude	3.16 (2.25)	3.41 (2.70)	*t*(55)=0.39	0.70	0.11	[-1.07, 1.58]
	P2	Deviant	Latency	185.58 (10.78)	182.12 (15.14)	*t*(55)=-0.99	0.33	-0.26	[-10.46, 3.54]

Note. Amplitude in μV, Latency (Lat) in milliseconds. SD = Standard Deviation; LP = Low-performance; HP = High-performance. Bold *p* values indicate significant values ($p > .05$).

Bayesian T-Tests

Table S2

Results of Bayesian Independent Samples t-tests Analysis of Group Difference (LP versus HP) in Amplitude (amp) and Latency (lat)

	Component	Condition	Amp/ lat	BF_{10}	BF_{01}	error%	95% CI
CPT	LPC	Match	Amplitude	**17.58**	0.057	7.159e-5	**[-1.376, -.242]**
	LPC	Match	Latency	0.305	3.277	0.016	[-.378, .618]
	LPC	Non-match	Amplitude	1.568	0.638	0.001	[-1.031, 0.031]
	LPC	Non-match	Latency	0.278	3.592	0.016	[-.501, .481]
	P2	Match	Amplitude	0.357	2.802	0.017	[-.668, .313]
	P2	Match	Latency	0.279	3.589	0.016	[-.481, .519]
	P2	Non-match	Amplitude	0.349	2.867	0.017	[-.675, .330]
	P2	Non-match	Latency	0.324	3.088	0.016	[-.359, .635]
Oddball	P3	Wave difference	Amplitude	0.917	1.091	0.013	[-.892, .099]
	P3	Wave difference	Latency	**5.795**	0.173	3.968e-6	**[.131, 1.189]**
	P2	Standard	Amplitude	0.294	3.402	0.007	[-.581, .372]
	P2	Standard	Latency	0.842	1.187	0.013	[-.133, .880]
	P2	Deviant	Amplitude	0.285	3.506	0.007	[-.560, .388]
	P2	Deviant	Latency	0.403	2.479	0.008	[-.251, .702]

Note. BF = Bayes Factors. CI = Credible Interval. Bayes factors were determined by Bayesian two-tailed independent t-tests. Substantial results are marked in bold.

Table S3

Results of Bayesian Independent Samples t-tests Analysis of Group Difference (LP versus HP) in Response time (RT) and D-prime for CPT Task

	BF_{10}	BF_{01}	error %
Response time	0.575	1.739	0.021
D-Prime	0.797	1.254	0.006

Note. BF = Bayes factors. Bayes factors were determined by Bayesian two-tailed independent t-tests. BF superior to 3 are considered substantial.

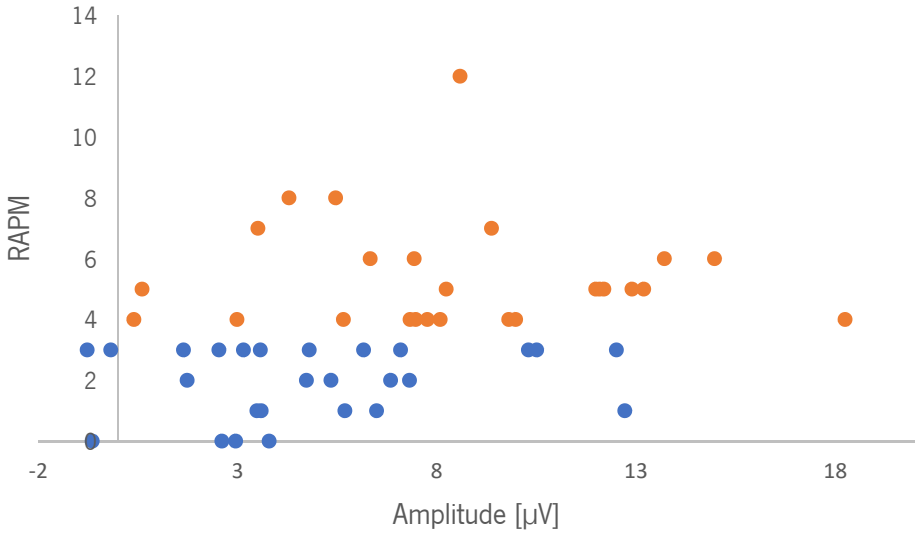

Figure S1. Scatter Plots showing the relationship between LPC amplitude of match stimuli and the RAPM (set 2). Red circle = HP. Blue circle = LP.

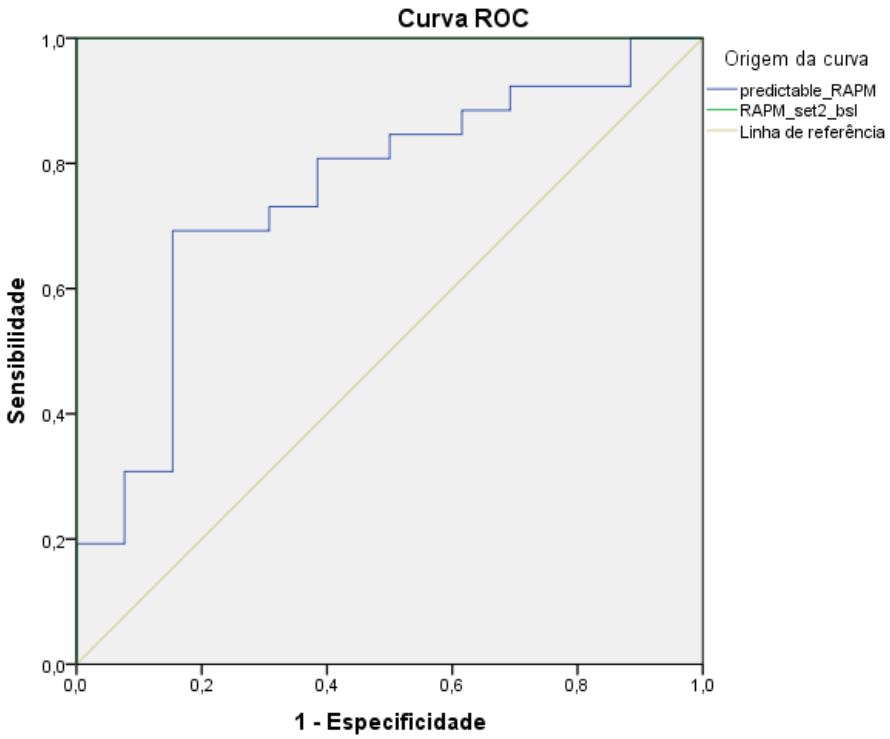

Figure S2. Receiver operating characteristic (ROC) curve for predicted scores of RAPM (set II).

CHAPTER VI

FINAL CONSIDERATIONS

Final considerations

The purpose of this section is to provide a general overview of the main results derived from this dissertation, highlighting the main achievements, challenges, limitations and future directions.

In Portugal more than 20% of people age 65 years or over (FFMS, 2018) and the prevalence of dementia is estimated to be 12.3% in people aging between 55 and 79 (Nunes et al., 2010) . In this context, where people are living longer, but not necessarily with quality of life (OECD/European Observatory on Health Systems and Policies, 2017), urge the need to promote means to maintain older people productive, healthy, and active and this was the main focus of the current dissertation.

In accordance, in the first study, we conducted a meta-analysis compiling experiments investigating the effects of working memory training (WMT) in healthy older adults. We found 27 experiments that met our inclusion criteria. To deal with multiple outcomes derived from the same study and the lack of reporting on correlation between measures and between pre- and post-testing, we performed a robust method of multilevel meta-analysis complemented with both a sensitivity analysis and the RVE method to confirm the robustness of our results. The efficacy of WMT to yield near transfer effects to working memory construct (but not for short-term memory) were verified, while far transfer to Gf was not observed. However, it is important to highlight that considering only studies using the Cattel test as far transfer outcome, the results became significant. Near transfer effects were maintained on follow-up but only for verbal WM. Nevertheless, only very few studies followed participants after training, which constitutes a limitation in the field, especially considering the delayed plasticity observed in the elderly (sleeper effects) (Borella, Cantarella, Carretti, De Lucia, & De Beni, 2019; Jaeggi, Buschkuehl, Shah, & Jonides, 2014). Moderator analysis pointed out the category of the outcome (i.e., Cattell and complex span), training length/duration in hours, number of sessions, and training type (i.e., mixed training), the type of control group (active versus passive) and the baseline performance as factors that may moderate transfer effects. Age and educational level were not significant moderators. These moderator variables may account for the mixed results found in the WMT field and should be taking into consideration in future studies.

Having reviewed the literature in WMT and found its potential to promote transfer restricted to WM domain, it was then necessary to unravel the results of studies addressing the combination of WMT and transcranial direct current stimulation (tDCS) in older people. Therefore, we performed a systematic

review to investigate the effects of tDCS on WM in healthy older adults. In general, the studies suggested that to apply tDCS over the pre-frontal or parietal cortex coupled with working memory tasks has the potential to modulate cognitive performance of both the trained task and transfer measures. Variables, such as level of education, modality of WM task (verbal or visuospatial) and time of assessment, emerged as potential moderators of the effects. However, only four studies met our criteria, pointing to the need for more investment in this area. This direct us to perform the third study. Additionally, no study had assessed the generalization of this intervention to Gf, a common practice in the field of WMT. Assessing generalization of gains is important to verify the training brought gains to other domains of functioning relevant in daily life (Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010). Gf is an important outcome in this sense because it is a predictor of functioning in many life achievements and it is associated with cognitive reserve (Aichele, Rabbitt, & Ghisletta, 2015; Gottfredson & Deary, 2004; Neisser et al., 1996).

Therefore, the third study was a double-blinded, randomized, sham controlled experiment in which we investigated the transfer effects of five-days of WMT combined with tDCS in healthy older people. Specifically, our experimental design had three arms: 1) training of dual n-back task + anodal tDCS (WMT+atDCS); 2) training of dual n-back task + sham tDCS (WMT+stDCS); 3) sham training (a visuoperceptual task) + sham tDCS (double-sham). The training task we have adopted was the dual *n*-back, which is a complex update task tapping simultaneously verbal and visuospatial modalities of WM. Updating ability is reduced in old age and it mediates age-related differences in Gf (Chen & Li, 2007). Also, older people seem to benefit most of updating training in comparison to the young population (Pergher, Wittevrongel, Tournoy, Schoenmakers, & Van Hulle, 2018). Therefore, we believed that training such a complex task could potentiate transfer effects, especially for Gf, in older adults. Indeed, considering near transfer effects, we verified that the atDCS+WMT group had a superior gain in verbal short-term memory (forward digit span) in comparison to the other two groups. Yet, the stDCS+WMT group had superior gains only in forward Corsi block tapping in comparison to the double-sham group, but the effects were not observed at follow-up. Considering the results of our meta-analysis (Teixeira-Santos, et. al., 2019), in which we verified near transfer effects of WMT for WM outcomes and not for short-term memory, we expected that near transfer effects were restricted to WM outcomes (the backward order of digit span). However, we observed the opposite pattern in which near transfer was verified only for short-term memory (forward digit span). This could be explained by the fact that the

backward order depends on a more demanding processing, requiring a much greater qualitative change in order to observe a change in its span in comparison to the forward digit span. This inconsistency with the meta-analytical study may also be due to the fact that in the meta-analysis the type of measure moderated the effects. More specifically, the gains were higher in studies using complex span than in studies using simple span. Additionally, we also assessed if our intervention could be generalized to Gf. In fact, atDCS+WMT was the only group who showed improvement in the RAPM, corroborating our initial hypothesis.

Additionally, factors have been suggested that may interact with the transfer effects, such as individual differences (Krause & Cohen Kadosh, 2014; Li, Uehara, & Hanakawa, 2015). Therefore, in this study, we tested moderator effects of the following variables in Gf: general cognitive ability at pretest (operationalized by the RAPM and vocabulary), age, and educational level. We choose the Raven score as outcome in this analysis, since it was the measure in which we verified the most robust far transfer gains, which in turn, is the measure that better allows to infer generalization of the intervention. In congruence with the results of our first study, none of these factors significantly moderated the results on Gf, challenging the moderator role of those variables in far transfer.

As we have identified methodological issues in the studies included in our meta-analysis[9], several aspects were considered to assure the validity of the results (Portney & Watkins, 2015). In accordance, we highlight the following characteristics of our study that meet these concerns: double-blindness (assessor and participant blinded); presence of follow-up; randomization; control conditions (sham tDCS/ sham training) and allocation concealment. However, taking into account all these aspects when designing our study posed several challenges. More specifically, to assure the blindness we had a second researcher to assess participants. For feasibility reasons, it was not possible to assure that the person applying tDCS was blinded.

Other challenge of this study was the fact that this experiment depended on equipment (i.e., tDCS and EEG), requiring more efforts from the team compared to studies of cognitive training without tDCS, pharmaceutic, home-based interventions or transversal studies. The difficulty was increased by the fact that we wanted to understand the effect of repeated sessions (i.e., 5 sessions) instead of a single session tDCS, having yet more six time-points for assessment.

[9] More specifically, most of the included studies did not give enough information that allows us to classify them as free of risk of bias

A further challenge was related to the recruitment. Given our inclusion/exclusion criteria, we had to exclude almost half of the older people. These participants did not score above the cut off for screening cognitive impairment and depression, or instead, were taking medication, had impaired auditory acuity, had history of neurological/psychiatric disorders or were taking psychotropic medication that could have a synergetic effect on tDCS. Due to the great number of participants excluded, a concern that occurred to me pertained to the external validity of it in terms of generalization for the Portuguese elderly population. Having such restrict inclusion criteria increased the internal validity but decreased external validity, as our sample does not broadly represent the older people in the current Portuguese scenario, especially in the north of Portugal (Paulo et al., 2011)., Additionally, the gender composition in our sample was asymmetrical, as it was difficult to recruit male participants, which caused an unbalance between the number of male and female ones. Recruitment issues also included the availability of the participants to attend 11 session in different places.

One limitation of this study is the lack of preregistration. Actually, we had started the preregistration in the Open Science Framework (OSF) (https://osf.io/dy3p8/). Nonetheless, due to the challenges involving preregistration (for a review, see Nosek, Ebersole, DeHaven, & Mellor, 2018; Veer & Giner-Sorolla, 2016), especially regarding set an *a priori* statistical analysis, we have not made the registration public. Therefore, the confirmatory approach of this study cannot be assured. Fortunately, preregistration is growing in the scientific field, from a total of 38 registration in OSF in 2012 to more than 12,000 in 2017 (Lindsay, 2018). Confirmatory research to validate the synergetic effect of tDCS combined with WM in elderly people is still necessary to validate this technique, especially because it has no approval for clinical use from several regulatory agencies around the world (for a review see Fregni et al., 2015).

Another limitation of this study was the fact that the sham task was not adaptive. In order for it to be more similar to the trained task, it could have had an adaptability criterion such as decreasing of stimulus time when the participants got more proficient in the task. Additionally, our study may lack statistical power since the *ad-hoc* sample size calculation was performed in G Power software (Faul, Erdfelder, Buchner, & Buchner, 2007) considering a traditional analysis of variance (ANOVA) method. Furthermore, follow-up time was short due to feasibility reasons. Finally, multiple tasks could be administered to assess the same construct in order to increase the validity of the measurement, as well as other measures that allow to verify the generalization of training to daily life.

Despite these limitations, the study has several important strengths, such as the analysis complemented by Bayesian methods and its experimental design, which had three conditions that allow the study of the effects of tDCS and WMT separately. Instead of using a passive control group, we included an active control task. This allowed the control of the effects resulting from social contact or the participants' expectations.

Additionally, a reflection that derived from this study is related to the zero-sum gain model theory (Brem, Fried, Horvath, Robertson, & Pascual-Leone, 2014; Fertonani & Miniussi, 2017). This approach states that gains associated with cognitive enhancement is also followed by losses in another domain due to the limited cognitive resources, following the physical principle of conservation of energy (Brem et al., 2014; Fertonani & Miniussi, 2017; Luber, 2014). In other words, transcranial electrical stimulation could benefit one cognitive system by reallocation of a limited resource, having a cost in a competing system (Iuculano & Cohen Kadosh, 2013). To illustrate, it is quite common to see a speed-accuracy trade-off in which higher accuracy may be achieved paying a processing speed cost (Leite et al., 2018). In our case, we identified this phenomenon when the atDCS+WMT group was the one that had negative effect sizes in the digit-symbol coding score (an index of processing speed) across assessment sessions, in comparison to the stDCS+WMT and the double placebo groups. Hereupon, it is important to, in addition to understand the real gains of stimulation, also verify the costs associated to it. In this light, it is important to foment the debate of the practical and ethical implications of using neuromodulation techniques in healthy population, the so-called "Cosmetic Neurology" (Chatterjee, 2004; Hamilton, Messing, & Chatterjee, 2011).

Finally, in our last study, we verified the physiological correlates of Gf in older people. The interest in the assessment of Gf in older adults was grounded its strong relation with health (e.g., risk of hospitalization due to psychological disorder; cardiovascular diseases; blood pressure; psychiatric disorders; dementia; life expectancy and brain reserve) (Aichele, Rabbitt, & Ghisletta, 2015; Deary, Weiss, & Batty, 2010; Gottfredson & Deary, 2004; Neisser et al., 1996; Schmand, Smit, Geerlings, & Lindeboom, 1997; Starr & Whalley, 2005). Therefore, Gf may be taken as an index of health in this population, even more reliable than subjective measures (Shakeel & Goghari, 2017). Thus, as we have adopted this measure as far transfer in the study 3, aimed to assess the neurophysiological correlates of Gf performance, as a way to complement our behavioral assessment with neurophysiological measures. Brain activity markers, such as ERPs, may allow us to understand the brain functioning

underling cognitive processing in healthy older population and, posteriorly, to identify suboptimal patterns of functioning that may not be early verified at a behavioral level. Therefore, the understanding of brain functioning through different brain markers may allow the early identification of people at risk of cognitive impairment or neurodegenerative disorders and enable the increment of therapeutic practices of prevention and earlier intervention for many age-related diseases (Jagust, 2013). As was recommended by the Futurage Project[10], an initiative to set a road map for ageing research in Europe, one of the research questions that should be addressed by researchers is related to the identification of early markers in aging (Walker, 2011). Therefore, our study aimed to assess whether late endogenous ERP components (i.e., P2, P300 and LPC) were associated with Gf in healthy elderly people. As a result, we found evidence of ERPs, specifically the LPC amplitude and the P300 latency, as indexes of Gf performance. Precisely, high-performance in Gf is associated with high LPC amplitudes and shorter P300 latencies. Similar results were found with young adults (Amin, Malik, Kamel, Chooi, & Hussain, 2015; Bazana & Stelmack, 2002; Beauchamp & Stelmack, 2006; De Pascalis, Varriale, & Matteoli, 2008; Jaušovec & Jaušovec, 2001; Wronka, Kaiser, & Coenen, 2013) and children (Duan, Shi, Sun, Zhang, & Wu, 2009; Schlottfeldt, Mansur-Alves, Flores-Mendoza, & Tierra-Criollo, 2018; Zhang et al., 2007; Zhang, Shi, Luo, Zhao, & Yang, 2006), but this study stands out for being the first to document this relationship in elderly people. These results have practical relevance, in particular in the context of clinical trials in WMT, which can incorporate those ERPs as a surrogate measurement related to the far transfer to Gf.

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CHAPTER VII

CONCLUSION

Conclusion

The aim of the present doctoral dissertation was to assess the transfer effects of working memory training (WMT) in healthy elderly people and the potential of the transcranial direct current stimulation (tDCS) to boost this intervention. Moderator analysis pointed out the category of the outcome (i.e., Cattell and complex span), training length/duration in hours, number of sessions, and training type (i.e., mixed training), the type of control group (active versus passive) and the baseline performance as factors that may moderate transfer effects. Age and educational level were not significant moderators. In addition, we characterized the electrophysiological correlates of Gf performance in older adults operationalized by the RAPM (Raven, Raven, & Court, 1998), a common far transfer outcome of WMT. We found that the ERPs could be used as a complement in the evaluation of WMT efficacy in elderly people.

To sum up, we raise specific concluding remarks derived from our results:

- WMT, alone or coupled with tDCS, may drive near transfer effects and the effects last longer after stimulation.
- There is no strong evidence supporting far transfer effects after WMT. However, when Cattell Test was used to assess Gf, the WMT effect became significant. Yet, the association between WMT and tDCS seems to favour far transfer effects to Gf.
- tDCS results were more evident at follow-up, which may be due to "sleeper effect", meaning that improvements in some cognitive domains take longer to manifest, especially in the case of older adults.
- The effects of WMT seem to be moderated by the adopted measures, type of training, training length and duration, baseline performance (only for visuospatial STM outcomes), and type of control group (only for visuospatial short-term memory). Baseline performance (in far transfer), age, educational level and general cognitive ability are not significant moderators of transfer effects.
- We verified that the P300 and late positive complex (LPC) ERPs are associated with Gf in healthy elderly people. More specifically, high performance is related to increased LPC amplitudes and shorter P300 latencies. Therefore, those ERP components worked as indexes to gauge Gf in older people and could be used to complement the

assessment in this population, especially as a surrogate measure in experiments assessing the effects of WMT.

Future directions

The present dissertation brought up to light specific aspects of the investigation onto WM interventions in the elderly that deserve further consideration in future studies. We carefully address those issues in the observations listed below:

- Given that we have demonstrated the relationship between ERPs and Gf, future studies should assess if the training has an effect in the P300 and LPC ERPs and explore the effects on EEG brain oscillations as well.
- It would be important to verify the impact of WMT associated with tDCS in a molecular level, such as in the brain-derived neurotrophic factor (BDNF) and the insulin-like growth factor-1 (IGF-1)[11]. In the context of this project, we have collected saliva from participants before and after the intervention. Our research team is now working on the validation of the saliva analysis protocol, as well as, verifying the relationship between these trophic factors with our outcomes. Later we will verify if the training had an impact on these factors.
- Futures studies could adopt other neural measurements to assess the neural mechanisms underlying training-related plasticity. For example, it could be verified if the training produces neural differentiation[12] WM performance.
- Future studies should also confirm the role of individual characteristics in WMT effects and tDCS, since we did not find substantial evidence to support it. Those studies could also considerer different contexts that have the potential to maximize the training effects (e.g., home-base *vs.* laboratory context; the importance of training feedback; group

[11] BDNF is associated with the main mechanisms of neuroplasticity (i.e., synaptogenesis, angiogenesis, and neurogenesis). IGF-1 is involved in neurogenesis and regulation of the BDNF gene and the deficiency of this protein could affect neurovascular coupling in the brain (Carro, Trejo, Busiguina, & Torres-Aleman, 2001; Murray & Holmes, 2011; Tarantini, Tran, Gordon, Ungvari, & Csiszar, 2017).
[12] Neural differentiation is the neural specificity of cortical regions to a given task, which is reduced in the elderly (Park et al., 2004). The lack of neural differentiation is postulated to be a mechanism associated to age-related cognitive decline (Li, Lindenberger, & Sikström, 2001).

format *vs.* individual interventions; the time of stimulation - online *vs.* offline; tDCS parameters and montages; different methods of transcranial electrical stimulation - i.e., transcranial alternating current stimulation or transcranial random noise stimulation).

As a consequence of these results, our research team is now performing an ongoing study in the context of the project "Getting the aging brain to train: a working memory and neurostimulation approach" assessing the effects of WMT on those ERPs.

Concluding remarks

We hope this PhD dissertation contributes to the development of the Translational Neuroscience research, in the cognitive stimulation and non-pharmacological interventions fields. Our data suggest that WMT is effective in producing a near transfer effect and tDCS worked as an add-on intervention in the promotion of far transfer to Gf. Moreover, we showed that the LPC amplitude and P3b latency might work as a putative marker of the Gf, supporting the use of these measures as outcomes to assess the effects of WMT. We believe that this can be a substantial contribution for the scientific community since it was the first study showing this association in older adults,

The understanding of neural mechanisms of healthy older people together with evidence of efficacy of cognitive enhancement techniques is a step forward to strengthen the available services of diagnosis, prevention, and treatment targeting this population.

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CONSENTIMENTO INFORMADO

Investigadora (aluna de Doutoramento): Ana Carolina Teixeira Santos
Orientadora: Professora Doutora Adriana da Conceição Soares Sampaio
Orientadora: Doutora Sandra Carvalho

Entidade Promotora: Laboratório de Neuropsicofisiologia, Centro de Investigação em Psicologia, Escola de Psicologia - Universidade do Minho

Designação do Estudo: *Getting the aging brain to train: a working memory and neurostimulation approach*

Caro participante,

Convidámo-lo a participar num estudo sobre os efeitos de sessões repetidas de ETCC associada ao treino cognitivo no envelhecimento, coordenado pela aluna de doutoramento Ana Carolina Santos e pelas professoras Adriana Sampaio e Sandra Carvalho, do Laboratório de Neuropsicofisiologia da Universidade do Minho.

Com este estudo pretendemos comprender melhor os efeitos da estimulação transcraniana por corrente contínua associada ao treino cognitivo e contribuir para a promoção do envelhecimento saudável. A sua participação é de elevada importância, visto que estará a prestar um contributo essencial no impulsionar do conhecimento científico no âmbito do envelhecimento.

Neste documento encontra-se informação relativa ao estudo. Por favor, fique à vontade para perguntar qualquer esclarecimento adicional que julgue necessário.

---

1. Objetivo:

O objetivo deste estudo é avaliar os efeitos do treino da memória operatória associado a sessões repetidas de ETCC sobre o córtex pré-frontal em idosos.

2. Descrição do estudo, procedimentos e duração:

O estudo será realizado em 9 sessões de aproximadamente 1 hora cada. Especificamente, nas duas primeiras sessões e nas duas últimas serão realizadas avaliações neuropsicológicas, recolha de dados de eletroencefalografia e recolha de saliva para análise dos níveis de BDNF. Nas 5 sessões intermediárias será realizado um treino cognitivo computadorizado conjuntamente com a aplicação da ETCC. O local das sessões poderá ser a Escola de Psicologia da Universidade do Minho ou na instituição a qual pertence.

A tarefa realizada no treino cognitivo será uma tarefa de memória operatória ou um treino de conhecimentos gerais. A memória operatória é um sistema responsável por reter, manipular e recuperar uma informação durante a realização de uma tarefa. Por exemplo, quando fazemos uma conta matemática mentalmente, é a memória operatória que nos permite manter os números na mente, enquanto realizamos a operação e produzimos uma resposta ao cálculo. Durante a execução desta tarefa, o participante receberá ETCC, ativa ou sham. O participante também responderá a questionários e escalas psicológicas antes e depois de cada sessão.

Informações acerca da ETCC

A ETCC é uma técnica de estimulação cerebral não invasiva que consiste na aplicação de uma corrente elétrica contínua de baixa intensidade no córtex cerebral, por meio de elétrodos colocados na cabeça. A ETCC é um procedimento seguro, indolor e facilmente tolerável, que tem se mostrado eficaz no tratamento de doenças de foro psiquiátrico e neurológico, bem como na melhoria do desempenho cognitivo e motor em diferentes populações.

Nesta experiência, serão colocados dois elétrodos no escalpe, inseridos em esponjas embebidas com soro fisiológico. Para identificação da área cerebral a ser estimulada serão realizadas medições anatómicas da cabeça com a utilizacão de uma fita métrica e será colocada uma marca temporária de caneta de feltro na cabeça para auxiliar na colocação dos elétrodos. A estimulação terá duração total de 20 minutos e durante toda a experiência o participante estará acompanhado por um profissional de Psicologia treinado em ETCC.

Informações acerca dos dados de eletroencefalografia

Uma parte do estudo envolverá a realização de um eletroencefalograma. Neste exame, elétrodos são colocados no couro cabeludo para registo da actividade elétrica cerebral. Estes eléctodros são ligados a um amplificador que permite detectar correntes elétricas muito pequenas. Este é um procedimento completamente não-invasivo. Enquanto a actividade cerebral estiver a ser registada, o participante irá realizar tarefas no computador que avaliam a memória operatória.

Informações acerca da recolha de saliva para avaliação dos níveis de BDNF

Neste estudo, os níveis de BDNF salivares e o polimorfirmos Val/Met COMT serão avaliados e relacionados com os efeitos da estimulação. Para tal, será feita uma recolha de saliva com recurso a um tubo graduado de Falcon. O procedimento é totalmente indolor e de fácil execução.

3. Riscos associados à participação na investigação:

Durante o início da estimulação, poderá sentir uma leve comichão ou formigueiro, que tende a diminuir ao longo da mesma. Dor de cabeça também poderá ser um efeito secundário da estimulação. Contudo, a ETCC geralmente é muito bem tolerada pelos participantes e não existem efeito adversos a longo prazo reportados até o momento. Ressalta-se que a ETCC não deve ser utilizada em pessoas que tenham metais sensíveis a campos elétricos, na cabeça ou noutra parte do corpo a uma distância inferior a 30 cm da cabeça.

4. Uso dos resultados de investigação e confidencialidade:

Será garatinda a confidencialidade e anonimato dos dados que serão utilizados apenas para fins científicos. Sendo de acesso exclusivo aos inverstigadores envolvidos no projeto.

5. Direitos do participante da investigação:

A participação no estudo é totalmente voluntária. O participante pode desistir a qualquer momento da realização da experiência, sem que isso envolva qualquer prejuízo para o mesmo.

Para maiores esclarecimentos, poderá contactar as investigadoras Ana Carolina Santos (aluna de doutoramento do Laboratório de Neuropsicofisiologia) ou Adriana Sampaio (diretora do Laboratório de Neuropsicofisiologia) através do número de telefone 253601398 ou através dos emails: adriana.sampaio@psi.uminho.pt , anacarolinatsantos@gmail.com.

Agradecemos sua atenção e valiosa colaboração e nos colocamos à disposição para qualquer esclarecimento.

Consentimento

Eu, _____,
declaro ter sido informado acerca dos objetivos, procedimentos, riscos e direitos dos participantes envolvidos neste estudo e concordo em participar voluntariamente do mesmo. Tive oportunidade de fazer as perguntas que julguei necessárias e para as quais tive respostas satisfatórias. Foi-me afirmado que tenho o direito de recusar a qualquer momento a minha participação no estudo, sem que isso possa envolver qualquer prejuízo na assistência que me é prestada.

Data: _____ / _____ / 2017

Assinatura do participante voluntário: _____

O Investigador,

*Assinatura:*_____

Data: _____ / _____ / 2017

Validação do cegamento:

Estudo:_____

Participante: _____

Por favor, responda às seguintes questões:

Você recebeu:

( ) Neuroestimulação placebo

( ) Neuroestimulação ativa

Quão confidente você está nessa resposta:

(1) Nada confiante
(2)
(3) Um pouco confiante
(4)
(5) Completamente confiante

Você acredita que a tarefa que realizou:

( ) Tarefa placebo

( ) Tarefa experimental

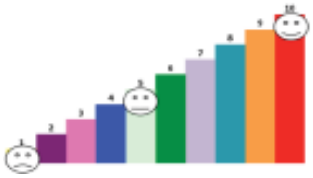
Quão confidente você está nessa resposta:

(1) Nada confiante
(2)
(3) Um pouco confiante
(4)
(5) Completamente confiante

Universidade do Minho
Escola de Psicologia

Escala Analógica Visual (VAS)
PRÉ ETCC/tRNS

Participante: _____ **Data:** ___/___/_____
Nome do estudo: _____
 # Visita: _____



0 = Ausência 5 = Moderado 10 = Máximo

1. **Sinto-me <u>cansado</u>(a).**

0 1 2 3 4 5 6 7 8 9 10

2. **Sinto-me <u>ansioso</u>(a).**

0 1 2 3 4 5 6 7 8 9 10

3. **Sinto-me <u>triste</u>(a).**

0 1 2 3 4 5 6 7 8 9 10

4. **Sinto-me <u>agitado</u>(a).**

0 1 2 3 4 5 6 7 8 9 10

5. **Sinto-me com <u>sono</u>.**

0 1 2 3 4 5 6 7 8 9 10

6. **Sinto <u>comichão</u>.**

0 1 2 3 4 5 6 7 8 9 10

7. **Sinto <u>cefaleia</u> (dor de cabeça).**

0 1 2 3 4 5 6 7 8 9 10

8. **Sinto <u>outro tipo de dor</u>.**

0 1 2 3 4 5 6 7 8 9 10

9. **Sinto <u>formigueiro</u>.**

0 1 2 3 4 5 6 7 8 9 10

10. **Sinto <u>um sabor metálico na boca.</u>**

Antes

0 1 2 3 4 5 6 7 8 9 10

Observações gerais: _____

_____
_____
_____
_____
_____

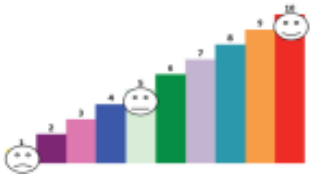
O investigador,

_____
(Nome, data, hora)

Universidade do Minho
Escola de Psicologia

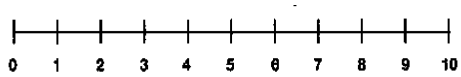
Escala Analógica Visual (VAS)
PÓS ETCC/tRNS

Participante: _____ **Data:** ___/___/_____
Nome do estudo: _____
 # Visita: _____

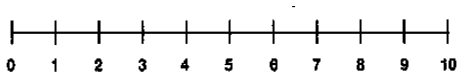


0 = Ausência 5 = Moderado 10 = Máximo

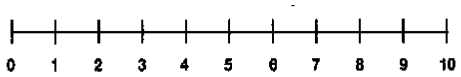
1. **Sinto-me cansado(a).**



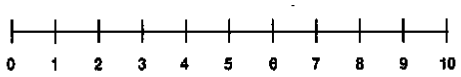
2. **Sinto-me ansioso(a).**



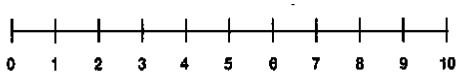
3. **Sinto-me triste(a).**



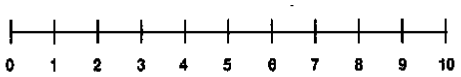
4. **Sinto-me agitado(a).**



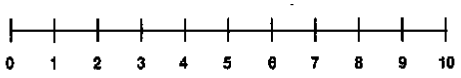
5. **Sinto-me com sono.**



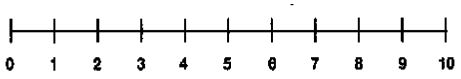
6. **Sinto comichão.**



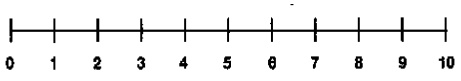
7. **Sinto cefaleia (dor de cabeça).**



8. **Sinto outro tipo de dor.**

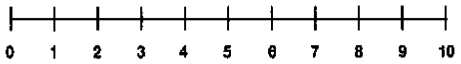


9. **Sinto formigueiro.**



10. **Sinto um sabor metálico na boca.**

Antes



Observações gerais: _____

_____
_____
_____
_____
_____

O investigador,

_____
(Nome, data, hora)

Data: ____/____/____

1. IDENTIFICAÇÃO:

Nome:_____

Idade: ____ Anos

Telefone:_____ **Email:** _____

Morada: _____

_____

Língua materna_____

Com quem vive? 1. Sozinho(a) ☐ 2. Cônjuge ☐ 3. Familiares (filhos/ irmãos / etc.) ☐
4. Amigo ☐ 5. Residentes do lar ☐ 6. Outro: _____

Escolaridade: Qual o último ano de escolaridade que frequentou?
1.Não frequentou escola ☐ 2. 4ºano ☐ 3. 6º ano ☐ 4. 9º ano ☐ 5. 12º ano ☐
6. Bacharelado ☐ 7. Licenciatura ☐ 8. Mestrado ☐ 9.Doutoramento ☐

Anos de escolaridade_____

Profissão: _____

Saúde – Sintoma ou queixa? Qual a severidade?

_____

_____

Dificuldade na vida diária? 1. Sim ☐ 2. Não ☐

_____

_____

Medicação (frequência, duração e dosagem).

_____

_____

_____

*Exclusão: L-DOPA, medicamentos anti-epilépiticos (Carbamazepina, oxcarbazepina, topiramato, carbamazepina, fenitoína, fenobarbital, lamotrigina, oxcarbazepina, primidona e valproato de sódio, carbamazepina, lamotrigina, fenobarbital, fenitoína, Ácido valpróico, Clonazepam, Estiripentol,

Felbamato, Fenitoína sódica, Fenobarbital, Fenobarbital sódico, Gabapentina, Lacosamida, Lamotrigina, Levetiracetam, Oxcarbazepina, Pregabalina, Primidona, Rufinamida, Cloridrato de tiagabina, Topiramato, Valproato de sódio, Valproato semisódico, Vigabatrina, Zonisamida).

Pratica atividade física? 1. Sim ☐ 2. Não ☐ Quantas horas por semana?_____

Estimulação cerebral (tDCS/TMS)? 1. Sim ☐ 2. Não ☐ teve alguma reação?_____

Antidepressivo? 1.Sim ☐ 2. Não ☐

Fuma? 1. Sim ☐ 2. Não ☐

Historial de doenças neurológica ou psiquiátrica

Condição médica	**1.Sim**	**2. Não**
Traumatismo craniano		
Tumores		
Demência		
Hipertensão		
Doencas infecciosas (eg. Ecefalite, Meningite)		
Epilepsia ou convulsões nos últimos dois anos		
Implantes cerebrais		
Anorexia nervosa		
Depressão		
Ferimento grave na cabeça		
Dores de cabeça frequente ou grave		
Dispositivos médicos implantados, como *pacemakers* cardíacos ou bombas médicas?		

Condição médica	**1.Sim**	**2. Não**
AVC (acidente vascular cerebral)		
Aneurisma		
Doenças cardíacas		
Abuso de drogas/ álcool		
Doenças degenerativas (e.g., esclerose múltipla, parkison)		
Perda de consciência nos últimos dois anos		
Diabetes Melitus		
Doença de Alzheimer		
Fobia		
Cirurgia na cabeça		
Doença que possa ter causado lesão cerebral?		
Metal na cabeça, como estilhaços, grampos cirúrgicos, ou fragmentos de soldagem?		

Outra(s)? Qual(is)?_____

Cartão de Jaeger.

Colocar o cartão a uma distância de 35 cm da pessoa idosa que se possuir óculos deve mantê-los durante o exame. A visão deve ser testada em cada olho em separado e depois em conjunto. Os olhos devem ser vendados com as mãos em forma de concha.

direita_____ esquerda_____ conjunto _____

Testar discriminação das letras e números.

Letra	**Sim**	**Não**	**Letra**	**Sim**	**Não**	**Letra**	**Sim**	**Não**	**Letra**	**Sim**	**Não**

GAI

Para algumas das afirmações que se seguem, pede-se a sua opinião sobre **o que tem sentido durante a última semana.** Se acha que o que é dito se aplica no seu caso, faça **uma cruz (X)** no quadrado **"Concordo"** se, pelo contrário, achar que o que é dito não aplica à sua situação, faça **uma cruz (X)** no quadrado **"Discordo".** Há ainda outras afirmações, que indicam a frequência com que determinadas coisas lhe podem ter acontecido na última semana, pede-se igualmente, que escolha a alternativa ("Concordo" ou "Discordo") que estiver mais próxima do que se passou contigo. **Responda, por favor, a todas as afirmações.** Não existem respostas certas ou erradas para estas afirmações porque as pessoas são diferentes umas das outras. O importante é responder de acordo com aquilo que sentiu (ou se passou contigo) **na última semana.**

	Concordo	Discordo
1. Ando preocupado (a) a maior parte do tempo.		
2. Tenho dificuldade em tomar decisões.		
3. Sinto-me muitas vezes inquieto (a).		
4. Tenho dificuldade em descontrair		
5. Muitas vezes não consigo apreciar as coisas por causa das minhas preocupações		
6. Aflijo-me muito com coisas sem importância.		
7. Sinto muitas vezes um peso na cabeça.		
8. Considero-me uma pessoa preocupada.		
9. Não consigo deixar de me preocupar mesmo com coisas simpes do dia-a-dia.		
10. Sinto-me muitas vezes nervoso.		
11. Muitas vezes os meus próprios pensamentos deixam-me ansioso (a).		
12. Sinto-me muitas vezes tenso (a).		
13. Penso que sou uma pessoa nervosa.		
14. Acho que vai sempre acontecer o pior.		
15. Sinto muitas vezes um nervosismo interior.		
16. Acho que as minhas preocupações interferem com a minha vida.		
17. Sinto-me muitas vezes paralisado (a) pelas minhas preocupações.		
18. Tenho muitas vezes a sensação de ter a cabeça vazia.		
19. Deixo de fazer coisas por me preocupar demasiado.		
20. Sinto-me muitas vezes aflito(a).		

Para que fosse possível diferenciar os indivíduos com ou sem indícios de ansiedade severa, foi empregue um ponto de corte de 09/08. O ponto de corte mencionado proporcionou uma sensibilidade de 0,89 e uma especificidade de 0,80 (Ribeiro et al., 2011).

The optimal cut-off point to detect severe anxiety
symptoms was 8/9, but no optimal cut-off point for Generalized Anxiety Disorder could be estimated.

Inventário de Lateralidade de Edimburgo

Por favor, indique as suas preferências no uso das mãos nas seguintes atividades, colocando uma + na coluna apropriada. Quando a preferência é tão forte que nunca tentará tentar utilizar a outra mão, a menos que forçado, coloque nas duas colunas. Se em alguma situação, for realmente indiferente, assinale com + em ambas as colunas. Em algumas das atividades listadas embaixo é requerido o uso de ambas as mãos. Nesses casos, a parte da tarefa, ou objeto, para a preferência pela mão requerida está indicada em parêntesis Por favor tente responder a todas as questões e deixe apenas em branco se não tiver qualquer experiência com o objeto ou tarefa.

	Mão direita		**Mão esquerda**	
Escrever				
Desenhar				
Atirar/Lançar				
Tesoura				
Escovar os dentes				
Faca (sem garfo)				
Colher				
Varrer (mão de cima)				
Acender um fósforo				
Abrir uma caixa (tampa)				
TOTAL				

D-E	
D+E	
(D-E/D+E)x100	

Abaixo de -40	**Esquerdino**
Entre -40 e +40	**Ambidestro**
Acima de +40	**Destro**

A cotação consiste em marcar "++" na coluna referente à mão que o sujeito indique utilizar e, caso este uso seja indiferente, marcar um "+" em ambas as colunas (Oldfield, 1971). Cada sinal "++" é contabilizado com 2 pontos e "+" com um ponto, o quociente de lateralidade pode variar entre -100 (preferência "fortemente esquerda") e +100 (preferência "fortemente direita") e, por fim, aplica-se a fórmula: QL= (D-E/D+E) x 100 (Oldfield, 1971)

GDS – Escala de Depressão Geriátrica de Yesavage

Traduzida e adaptada por Margarida Pocinho, Carlos Amaral Dias, Carlos Farate (2005)

	Sim	Não
1- Está satisfeito com a vida actual		
2- Abandonou muitas das suas atividades e interesses		
3- Sente-se que a sua vida está vazia		
4- Anda muitas vezes aborrecido		
5- Encara o futuro com esperança		
6- Tem pensamentos que o incomoda e não consegue afastar		
7- Sente-se animado e com boa disposição a maior parte do tempo		
8- Anda com medo que lhe vá acontecer alguma coisa má		
9- Sente-se feliz a maior parte do tempo		
10- Sente-se muitas vezes desamparado ou desprotegido		
11- Fica muitas vezes inquieto e nervoso		
12- Prefere ficar em casa, em vez de sair e fazer outras coisas		
13- Anda muitas vezes preocupado com o futuro		
14- Acha que tem mais problemas de memória do que as outras pessoas		
15- Actualmente, sente-se muito contente por estar vivo		
16- Sente-se muitas vezes desanimado e abatido		
17- Sente que, nas condições atuais, é um pouco inútil		
18- Preocupa-se muito com o passado		
19- Sente-se cheio de interesse pela vida		
20- Custa-lhe muito meter-se em novas atividades		
21- Sente-se cheio de energia		
22- Sente que para a sua situação não há qualquer esperança		
23- Julga que a maior parte das pessoas passa bem melhor do que o senhor		
24- Aflige-se muitas vezes por coisas sem grande importância		
25- Dá-lhe muitas vezes vontade de chorar		
26- Sente dificuldade em se concentrar		
27- Evita estar em locais onde estejam muitas pessoas (reuniões sociais)		
Total		

Ausência de depressão >=10

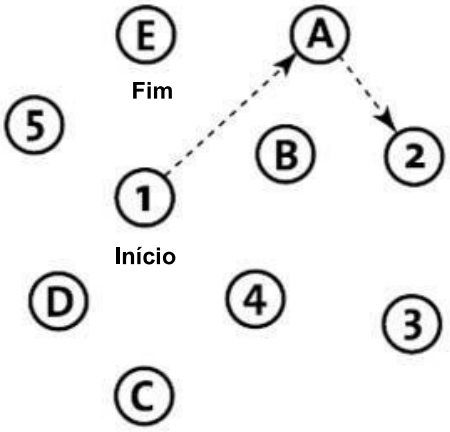
Lembrar aos participantes para evitar o consumo de café, de tabaco e de álcool antes das sessões.

MONTREAL COGNITIVE ASSESSMENT (MOCA)

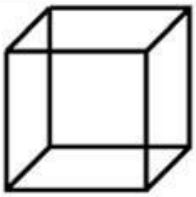
VERSÃO PORTUGUESA – 7.1 VERSÃO ORIGINAL

Nome: _____ **Idade:** _____
Género: _____ **Data de Nascimento:** _____
Escolaridade: _____ **Data de Avaliação:** _____

VISUO-ESPACIAL / EXECUTIVA



Copiar o cubo



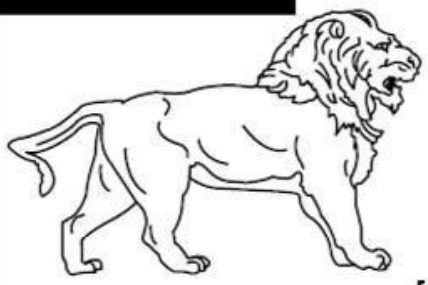
[ ] [ ]

Desenhar um Relógio (onze e dez) (3 pontos)

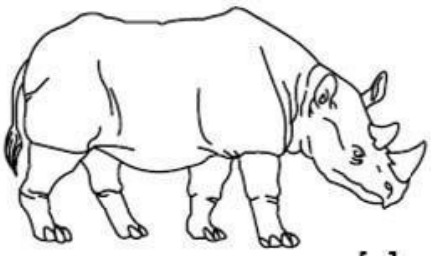
[ ] Contorno [ ] Números [ ] Ponteiros

Pontos ___/5

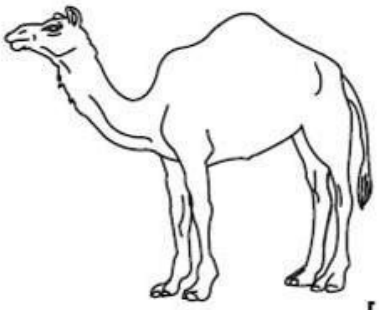
NOMEAÇÃO



[ ]



[ ]



[ ]

___/3

MEMÓRIA

Leia a lista de palavras. O sujeito deve repeti-la. Realize dois ensaios. Solicite a evocação da lista **5 minutos mais tarde.**

	Boca	Linho	Igreja	Cravo	Azul
1º ensaio					
2º ensaio					

Sem Pontuação

ATENÇÃO

Leia a sequência de números. (1 número/segundo)

O sujeito deve repetir a sequência. [ ] 2 1 8 5 4

O sujeito deve repetir a sequência na ordem inversa. [ ] 7 4 2

___/2

Leia a série de letras (1 letra/segundo). O sujeito deve bater com a mão cada vez que for dita a letra A. Não se atribuem pontos se ≥ 2 erros.

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

___/1

Subtrair de 7 em 7 começando em 100. [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 ou 5 subtracções correctas: **3 pontos;** 2 ou 3 correctas: **2 pontos;** 1 correcta: **1 ponto;** 0 correctas: **0 pontos**

___/3

LINGUAGEM

Repetir: Eu só sei que hoje devemos ajudar o João. [ ] **O gato esconde-se sempre que os cães entram na sala.** [ ]

___/2

Fluência verbal: Dizer o maior número possível de palavras que comecem pela letra "P" (1 minuto). [ ] _____ (N ≥ 11 Palavras)

___/1

ABSTRACÇÃO

Semelhança p.ex. entre banana e laranja = fruta [ ] **comboio - bicicleta** [ ] **relógio - régua**

___/2

EVOCAÇÃO DIFERIDA

		Boca	Linho	Igreja	Cravo	Azul	
	Deve recordar as palavras SEM PISTAS	[ ]	[ ]	[ ]	[ ]	[ ]	Pontuação apenas para evocação **SEM PISTAS**
Opcional	**Pista de categoria**						
	Pista de escolha múltipla						

___/5

ORIENTAÇÃO

[ ] **Dia do mês** [ ] **Mês** [ ] **Ano** [ ] **Dia da semana** [ ] **Lugar** [ ] **Localidade**

___/6

© Z.Nasreddine MD

Examinador: _____

TOTAL ___/30

Versão Portuguesa: Freitas, S., Simões, M. R., Santana, I., Martins, C. & Nasreddine, Z. (2013). *Montreal Cognitive Assessment (MoCA): Versão 1.* Coimbra: Faculdade de Psicologia e de Ciências da Educação da Universidade de Coimbra.

Universidade do Minho

SECVS

Subcomissão de Ética para as Ciências da Vida e da Saúde

Identificação do documento: SECVS 012/2016 (ADENDA)

Título do projeto: *Getting the aging brain to train: a working memory and neurostimulation approach*

Investigador(a) responsável: Doutora Adriana Sampaio, Centro de Investigação em Psicologia (CIPsi), Escola de Psicologia, Universidade do Minho; Doutora Sandra da Conceição Ribeiro de Carvalho, do Spaulding Labuscagne Neuromodulation Center, do Spaulding Rehabilitation Hospital, EUA; e Ana Carolina Teixeira Santos, aluna do programa de Doutoramento em Psicologia Básica da Universidade do Minho

Subunidade orgânica: Laboratório de Neuropsicofisiologia, Centro de Investigação em Psicologia, Escola de Psicologia - Universidade do Minho

Outras Unidades: Spaulding Neuromodulation Center, Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA, USA; Department of Physical Medicine and Rehabilitation, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

PARECER

A Subcomissão de Ética para as Ciências da Vida e da Saúde (SECVS) analisou o processo relativo ao pedido de adenda ao projeto intitulado *"Getting the aging brain to train: a working memory and neurostimulation approach".*

As alterações, para as quais se pede Parecer são:

- Alteração do título do projeto de "Efeitos de sessões repetidas da estimulação transcraniana por corrente contínua (ETCC) associada ao treino da memória operatória no envelhecimento - análise combinada de medidas comportamentais e neurofisiológicas" para "Getting the aging brain to train: a working memory and neurostimulation approach".
- Análise de BDNF feita pela coleta de saliva dos participantes (aspeto descrito no protocolo inicial, mas não contemplado no Parecer inicial)
- Adição de um estudo com ressonância magnética, de componente estrutural e funcional (sem tarefa)

Assegura-se que os compromissos de boas práticas na investigação dadas pelo IR do estudo e por outros investigadores ou colaboradores na investigação, incluindo garantias de confidencialidade, continuarão a ser seguidas. Apresentou-se o protocolo de investigação com fundamentação teórica e metodológica para as alterações ao protocolo original supracitadas.

Os documentos apresentados revelam que o projeto obedece aos requisitos exigidos para as boas práticas na experimentação com humanos, em conformidade com o Guião para submissão de processos a apreciar pela Subcomissão de Ética para as Ciências da Vida e da Saúde.

Face ao exposto, a SECVS nada tem a opor à realização do projeto.

Braga, 29 de setembro de 2016.

A Presidente

MARIA CECÍLIA DE LEMOS PINTO ESTRELA LEÃO

Digitally signed by MARIA CECÍLIA DE LEMOS PINTO ESTRELA LEÃO
DN: c=PT, o=Cartão de Cidadão, ou=Cidadão Português, ou=Assinatura Qualificada do Cidadão, sn=DE LEMOS PINTO ESTRELA LEÃO, givenName=MARIA CECÍLIA, serialNumber=BI014512203, cn=MARIA CECÍLIA DE LEMOS PINTO ESTRELA LEÃO
Date: 2016.09.30 14:33:55 +01'00'

Maria Cecília de Lemos Pinto Estrela Leão

Universidade do Minho

SECVS

Identificação do documento: SECVS 012/2016 (ADENDA)

Título do projeto: *Getting the aging brain to train: a working memory and neurostimulation approach*

Investigador(a) responsável: Doutora Adriana Sampaio, Centro de Investigação em Psicologia (CIPsi), Escola de Psicologia, Universidade do Minho; Doutora Sandra da Conceição Ribeiro de Carvalho, do Spaulding Labuscagne Neuromodulation Center, do Spaulding Rehabilitation Hospital, EUA; e Ana Carolina Teixeira Santos, aluna do programa de Doutoramento em Psicologia Básica da Universidade do Minho

Subunidade orgânica: Laboratório de Neuropsicofisiologia, Centro de Investigação em Psicologia, Escola de Psicologia - Universidade do Minho

Outras Unidades: Spaulding Neuromodulation Center, Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA, USA; Department of Physical Medicine and Rehabilitation, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Data de receção na SECVS: 30 de agosto de 2016

Grelha de Verificação

Processo submetido em suporte: [X] eletrónico [ ] físico (em papel)

Documentos	Sim	Não	Não se aplica
Requerimento e/ou ofício e/ou pedido de apreciação de projeto [a) b)]	X		
Informação do Responsável pela Unidade/Diretor de Serviço sobre apoio e/ou enquadramento/cabimento do projeto na Unidade/Serviço em que decorrerá [a) b)]	X		
Protocolo do estudo, incluindo, se aplicável, os instrumentos de recolha de dados e/ou informação para o participante [a) b)]	X		
Curriculum Vitae abreviado do Investigador Responsável [a) b)]	X		
Modelo de Consentimento Informado [a) b)]	X		
Modelo de Declaração de Compromisso de Confidencialidade	X		
Informação sobre financiamento para o cumprimento do projeto, incluindo, se aplicável, cabimento/inscrição no orçamento da Unidade/Serviço em que decorrerá e/ou com fonte de financiamento nacional/internacional	X		
CESHB – Remitir processo: Sim [ ] Não [X]			
Requerimento dirigido ao Presidente da CESHB [b)]		X	
Formulário da CESHB devidamente preenchido [b)]		X	
Outros			
Autorizações e/ou Pareceres de (Sub)Comissões de Ética	X		

Acordo Financeiro		X	
Apólice de Seguro		X	
Informação do Orientador da Tese sobre apoio e/ou enquadramento do projeto		X	

[a] Documentos obrigatórios de acordo com as normas orientadoras para submissão de processos a apreciar pela SECVS em Anexo ao Despacho RT-76/2012 que estabelece as regras de atuação e funcionamento da mesma.
[b] Documentos obrigatórios de acordo com o funcionamento da Comissão de Ética para a Saúde do Hospital de Braga (CESHB).

Justificação de alteração a protocolo inicial

Trata-se de um pedido de alteração ao protocolo inicial do estudo "Efeitos de sessões repetidas da estimulação transcraniana por corrente contínua (ETCC) associada ao treino da memória operatória no envelhecimento - análise combinada de medidas comportamentais e neurofisiológicas" com aprovação da SECVS a 27 de junho de 2016.

Foi submetido o protocolo de investigação, sendo efetuado um pedido de emenda do título e método do projeto de pesquisa supracitado para as quais se pede Parecer:

- Alteração do título do projeto para "Getting the aging brain to train: a working memory and neurostimulation approach";

- Análise de BDNF feita pela coleta de saliva dos participantes (aspeto descrito no protocolo inicial, mas não contemplado no Parecer inicial);

- Adição de um estudo com ressonância magnética, de componente estrutural e funcional (sem tarefa).

Assegura-se que os compromissos de boas práticas na investigação dadas pelo IR do estudo e por outros investigadores ou colaboradores na investigação, incluindo garantias de confidencialidade, continuarão a ser seguidas. Apresentou-se em anexo o protocolo de investigação com fundamentação teórica e metodológica para as alterações ao protocolo original supracitadas.

Indica-se que o estudo deverá solicitar Parecer e/ou autorização e seguir as diretivas nacionais e/ou locais de cada lugar de recolha, como aplicável, particularmente das Unidades Hospitalares e/ou Unidades de Saúde onde será realizado e/ou onde serão recolhidas as amostras e/ou dados e/ou aplicados os questionários, se aplicável.

Os documentos enviados estão em conformidade com o Guião para submissão de processos a apreciar pela Subcomissão de Ética para as Ciências da Vida e da Saúde (SECVS).

Face ao exposto, nada temos a opor à execução do projeto.

Braga, 29 de setembro de 2016

A Presidente

MARIA CECÍLIA DE LEMOS PINTO ESTRELA LEÃO

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Date: 2016.09.30 14:28:41 +01'00'

Maria Cecília de Lemos Pinto Estrela Leão