TESE DE DOUTORAMENTO

CAMBIOS RELACIONADOS COA IDADE NA ACTIVIDADE ELÉCTRICA CEREBRAL DIANTE DUNHA TAREFA DE MEMORIA DE TRABALLO VISO-ESPACIAL

Asdo.....

Diego Pinal Fernández

PROGRAMA DE DOUTORAMENTO EN NEUROCIENCIA

FACULTADE DE PSICOLOXÍA

SANTIAGO DE COMPOSTELA

2015

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

FACULTADE DE PSICOLOXÍA
Dpto. de Psicoloxía Clínica e Psicobioloxía

Campus universitario sur ● 15782 Santiago de Compostela
Tfno.: 981 563 100 ● Fax: 981 528 071

INFORME DOS DIRECTORES DA TESE

D. Fernando Díaz Fernández e Dna. Montserrat Zurrón Ocio, profesores do Departamento de Psicoloxía Clínica e Psicobioloxía;

Como Directores da Tese de Doutoramento titulada

"Cambios relacionados coa idade na actividade eléctrica cerebral diante dunha tarefa de memoria de traballo viso-espacial"

Presentada por D. Diego Pinal Fernández

Alumno do Programa de Doutoramento de Neurociencias.

Autorizamos a presentación da tese indicada, considerando que reúne os requisitos esixidos no artigo 33 do regulamento de Estudos de Doutoramento, así como os recollidos no artigo 40 de dito regulamento para a Mención Internacional do título de Doutor, e que como Directores da mesma non incorre nas causas de abstención establecidas na lei 30/1992.

Asdo.....

Fernando Díaz Fernández

Asdo.....

Montserrat Zurrón Ocio

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

AGRADECEMENTOS

En primeiro lugar gustaríame darlle as grazas a Fernando Díaz e Montserrat Zurrón, eles déronme esta oportunidade, creron en min e soubéronme apoiar, dirixir e aconsellar neste longo camiño que hoxe por fin ve o seu froito. Grazas tamén por ser como sodes, ás veces é tan importante nun traballo as tarefas que se fan, como as persoas coas que se fan. Así pois haberá coñecementos e aprendizaxes que, non estando relacionados coa psicofisioloxía, teñen o seu valor para a vida.

Tamén quero expresar a miña gratitude a quen me aceptaron nos seus laboratorios (incluso dúas veces!!) e exerceron de grandes mestres para min. Grazas polo voso cariño e afecto, e tamén pola vosa infinda paciencia comigo. Vaia pois o meu recordo para Merchi e Jose Luis en Sevilla e para Paul e Annette en Guildford.

Non podo esquecerme de todos os compañeiros que tiven tanto aquí como acolá. Grazas por facer que todos os días puidese vir a traballar cun sorriso e con ilusión, e por formar parte de esas pequenas cousas marabillosas do día a día. Foi un pracer pertencer a ese "comando" de xentes de ciencia que se abre paso nun tempo desfavorable. Ademais, agardo que esa loita continúe por moitos anos.

Nembargantes, todo escomezou moito antes de ter chegado sequera a Universidade. Nunca darei coas palabras axeitadas para expresar o moito que quero a miña familia. De non ser por vos, xamais tería escrito esta páxina, na tese, nin na miña vida.

Gustaríame agradecerlle tamén todo o que me dan a quen comparten a vida comigo. A Inma, grazas, simplemente, porque con todo o que poda dicir sempre deixarei algo atrás. E a Garba, grazas por estar aí, por acompañarme nas interminables horas diante da pantalla do ordenador e polo calor que lle das ó fogar.

E por último, grazas amigos por crer en min, por apoiarme, por facerme rir e sorrir, por sentir o que eu sentía, polo consello, pola compañía, polos momentos, polos comandos e as comandas, grazas por ser vos.

GRAZAS!!

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

Cambios relacionados coa idade na actividade eléctrica cerebral diante dunha tarefa de memoria de traballo viso-espacial.

RESUMO

O declive das capacidades cognitivas asociado á idade afecta principalmente á memoria de traballo viso-espacial, polo que afondar no coñecemento sobre os seus aspectos básicos e a súa evolución ó longo da vida é esencial para xerar intervencións que propicien melloras na calidade de vida dos maiores. Consecuentemente, nesta tese de doutoramento analizouse o sinal electroencefalográfico durante a codificación, mantemento e recuperación da información en memoria de traballo viso-espacial. Deste xeito, estudouse tanto a estrutura temporal da actividade eléctrica cerebral, e a súa modulación por manipulacións da carga en memoria e da duración do mantemento; como o impacto do avellentamento en dita actividade. Os resultados amosaron que a estrutura temporal da actividade eléctrica cerebral durante a codificación e recuperación é semellante, abranguendo dende procesos perceptivos ata procesos post-categorización do estímulo. Manipulacións da carga en memoria modularon a asignación de recursos de procesamento para procesos de avaliación e categorización dos estímulos, así como para procesos post-categorización. En tanto que as manipulacións da duración do mantemento, modularon os recursos de procesamento recrutados por procesos perceptivos e de avaliación estimular durante a recuperación. Pola súa parte, o mantemento de información caracterizouse por un aumento da inhibición en áreas cerebrais irrelevantes para a tarefa, concorrente cunha redución dependente da carga na inhibición en áreas relevantes. En canto ó avellentamento, existe unha diminución da velocidade en diferentes aspectos da avaliación estimular durante a codificación e a recuperación. Tamén se observou maior dependencia do recrutamento dos recursos de procesamento frontais en relación ós parietais nos maiores. Amais, durante o mantemento de información apreciouse unha ineficiente coordinación, asociada á idade, das redes neurais relevante e irrelevante para a tarefa, que se caracterizou por un déficit na inhibición da rede irrelevante para a tarefa, asociado co deterioro da execución condutual.

PALABRAS CHAVE

Memoria de traballo; avellentamento; EEG; carga en memoria; duración do mantemento.

Cambios relacionados con la edad en la actividad eléctrica cerebral ante una tarea de memoria de trabajo viso-espacial.

RESUMEN

El declive de las capacidades cognitivas asociado a la edad afecta principalmente a la memoria de trabajo viso-espacial, por lo que ahondar en el conocimiento sobre sus aspectos básicos y su evolución a lo largo de la vida es esencial para generar intervenciones que propicien mejoras en la calidad de vida de los mayores. Consecuentemente, en esta tesis doctoral se analizó la señal electroencefalográfica durante la codificación, mantenimiento y recuperación de información en memoria de trabajo, para estudiar tanto la estructura temporal de la actividad eléctrica cerebral, y su modulación por la carga en memoria y la duración del mantenimiento; como el impacto del envejecimiento en dicha actividad. Los resultados mostraron que la estructura temporal de esta actividad durante la codificación y recuperación es similar, comprendiendo desde procesos perceptivos hasta procesos post-categorización del estímulo. Manipulaciones de la carga en memoria modularon la asignación de recursos a procesos de evaluación y categorización de los estímulos, así como a procesos post-categorización; y las manipulaciones de la duración del mantenimiento, los recursos reclutados por procesos perceptivos y de evaluación estimular durante la recuperación. Por su parte, el mantenimiento de información se caracterizó por un aumento de la inhibición en áreas cerebrales irrelevantes para la tarea, concurrente con una reducción dependiente de la carga en la inhibición en áreas relevantes. En cuanto al envejecimiento, existe un enlentecimiento en diferentes aspectos de la evaluación estimular durante la codificación y recuperación. También, se observó mayor dependencia del reclutamiento de recursos frontales en relación con los parietales en los mayores. Además, durante el mantenimiento se apreció una ineficiente coordinación, asociada a la edad, de las redes neurales relevante e irrelevante para la tarea, que se caracterizó por un déficit en la inhibición de la red irrelevante, asociado con el deterioro de la ejecución.

PALABRAS CLAVE

Memoria de trabajo; envejecimiento; EEG; carga en memoria; duración del mantenimiento.

Age-related changes in brain electrical activity to a visuospatial working memory task.

ABSTRACT

Age-related declines in cognitive capacities specially affect visuospatial working memory. Therefore, deepen in the understanding of its basic aspects as well as in its evolution throughout the lifespan is essential to generate interventions that favor improvements in the quality of life of old adults. Consequently, in this doctoral thesis electroencephalographic signals were analyzed during encoding, maintenance and retrieval of information in visuospatial working memory. This enables the study of the time course of brain electrical activity and its modulation by memory load and maintenance duration manipulations, as well as the impact of aging on the aforementioned activity. Results revealed that the temporal structure of brain electrical activity during encoding and retrieval is similar and comprised from perceptual to post-categorization processes. Memory load manipulations modulated the allocation of processing resources to processes related with stimulus evaluation and categorization, and for post-categorization processes too. Regarding maintenance duration manipulations, they modulate the recruitment of processing resources by perceptual and stimulus evaluation processes during information retrieval. In addition, information maintenance was characterized by an increase in the inhibition of processing in task-irrelevant brain areas, which was concurrent to a memory load dependent reduction in the inhibition of processing in task relevant areas. Finally, as regards the impact of aging, a slowing of processing speed in different components related with stimulus evaluation was observed during encoding and retrieval. Also, a greater reliance in the recruitment of frontal in relation to parietal processing resources was observed in old than young adults. Additionally, during maintenance of information an age-related inefficient coordination of task-relevant and task-irrelevant functional brain networks was found, which was characterized by a deficit in the inhibition of the task-irrelevant network, and associated with the decline in task performance.

KEYWORDS

Working memory; aging; EEG; memory load; maintenance duration.

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

PUBLICACIÓNS DERIVADAS DO TRABALLO DE DOUTORAMENTO

Artigos en revistas internacionais

- **Pinal, D**., Zurrón, M. & Díaz, F. (2014). Effects of load and maintenance duration on the time course of information encoding and retrieval in working memory: from perceptual analysis to post-categorization processes. *Frontiers in Human Neuroscience, 8* (Article 165). doi:10.3389/fnhum.2014.00165.

    - Revista incluída no JCR. Factor de impacto (2013): 2.895 (5 anos): 3.268
    - Edición de ciencias; Psicoloxía Q2 (24/74)
    - Número de veces citado segundo ISI Web of Science: 0
    - Número de veces citado segundo Google Académico: 2

- Crespo-García, M., **Pinal, D**., Cantero, J. L., Díaz, F., Zurrón, M. & Atienza, M. (2013). Working Memory Processes Are Mediated by Local and Long-range Synchronization of Alpha Oscillations. J*ournal of Cognitive Neuroscience, 25*(8), 1343-1357. doi:10.1162/jocn_a_00379.

    - Revista incluida no JCR. Factor de impacto (2013): 4.687 (5 anos): 5.705
    - Edición de ciencias sociais; Psicoloxía, experimental Q1 (4/83).
    - Edición de ciencias; Neurociencia Q1 (52/251)
    - Número de veces citado segundo ISI Web of Science: 2
    - Número de veces citado segundo Google Académico: 3

- **Pinal, D**., Zurrón, M. & Díaz, F. (under review in Frontiers in Aging Neuroscience). Age-related changes in brain activity are specific for high order cognitive processes during successful encoding of information in working memory.
- **Pinal, D.**, Zurrón, M. & Díaz, F. (submitted to Journal of Gerontology Series A Biological Sciences). An ERP Study of the Effects of Age, Load and Maintenance Duration on Working Memory Recognition.
- **Pinal, D**., Zurrón, M., Díaz, F. & Sauseng, P. (accepted for publication in Neurobiology of Aging). Stuck in Default Mode: Inefficient Cross-Frequency Synchronization May Lead to Age-Related Short-Term Memory Decline. 10.1016/j.neurobiolaging.2015.01.009.

    - Revista incluida no JCR. Factor de impacto (2013): 4.853 (5 anos): 5.127
    - Edición de ciencias; Xeriatría e xerontoloxía Q1 (4/49)
    - Número de veces citado segundo ISI Web of Science: 0
    - Número de veces citado segundo Google Académico: 0

Actas de congresos en revistas internacionais

- **Pinal, D**., Zurrón, M. & Díaz, F. (2011). ERP differences between encoding and retrieval in a visuospatial working memory task. Frontiers in Human Neuroscience Conference Abstract: XI International Conference on Cognitive Neuroscience (ICON XI). doi:10.3389/conf.fnhum.2011.207.00219.

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

Abbreviations

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

µV	Microvolts.
a.u.	Arbitrary Unit.
Acc	Accuracy.
ACC	Anterior Cingulate Cortex.
ACG	Anterior Cingulate Gyrus.
ACP	*Análise de Compoñentes Principais.*
Amp	Amplitude.
ANOVA	Analysis Of Variance.
BA	Brodmann Area.
BOLD	Blood-Oxygen Level Dependent.
BR	Ratios of Salience to Bootstrap Standard Errors.
BVA	Brain Vision Analyzer.
CA	California.
CCA	Córtex Cingulado Anterior.
cm	Centimeter.
dB	Decibel.
DI	Dissimilarity Index.
DLPFC	Dorsolateral Prefrontal Cortex.
DMN	Default Mode Network.
DMS	Delayed Match to Sample.
doi	Digital Object Identifier.
E	Elderly.
ED	*Emparellamento Demorado.*
EEG	Electroencephalogram.
e.g.	Exempli Gratia (Latin).
EI	*Eficiencia Inversa*
eLORETA	exact Low Resolution brain Electromagnetic Tomography.
EOG	Electrooculogram.

Eq.	Equation.
ERP	Event Related Potential.
EU	European Union.
FEF	Frontal Eye Fields.
FEW	Familywise Error.
FFT	Fast Fourier Transform.
Fig	Figure.
fMRI	functional Magnetic Resonance Imaging.
HEOG	Horizontal Electrooculogram.
HL	High (memory) Load.
Hz	Hertz.
ICA	Independent Component Analysis.
IE	Inverse Efficiency.
i.e.	Id Est (Latin).
IFG	Inferior Frontal Gyrus.
Inc.	Incorporation.
INE	*Instituto Nacional de Estadística.*
IPL	Inferior Parietal Lobe.
ITG	Inferior Temporal Gyrus.
IPS	Intraparietal Sulcus.
kΩ	Kiloohm.
L	Left.
Lat	Latency.
LMP	Long Maintenance Period.
LL	Low (memory) Load.
LORETA	Low Resolution brain Electromagnetic Tomography.
m	Meter.
max	Maximum.

MEG	Magnetoencephalography.
MFG	Middle Frontal Gyrus.
min	Minimum.
Mm	Millimeter.
MNI	Montreal Neurological Index.
ms/msec	Millisecond.
MT	*Memoria de Traballo.*
MTL	Medial Temporal Lobe.
NP	Normalized Power.
nPLI	normalized Phase Lag Index
NSW	Negative Slow Wave.
p	Probability (associated).
p.	Page.
PAC	Phase:Amplitude Coupling.
PASA	Posterior to Anterior Shift in Aging.
páx.	*Páxina.*
PCA	Principal Component Analysis.
PE	*Potencial Evocado.*
PET	Positron Emission Tomography.
PFC	PreFrontal Cortex.
PLI	Phase Lag Index.
PLS	Partial Least Squares.
PPC	Posterior Parietal Cortex.
PSW	Positive Slow Wave.
R	Right.
RDI	Rexión de Interese
ROI	Region of Interest.
RT	Reaction Time.

s	Second.
SEM	Standard Error of the Mean.
SFG	Superior Frontal Gyrus.
sLORETA	standard Low Resolution brain Electromagnetic Tomography.
SMP	Short Maintenance Period.
SNPM	Statistical Non-Parametric Mapping.
SPL	Superior Parietal Lobe.
STM	Short-Term Memory.
TANOVA	Topographic Analysis of Variance/map-to-map comparison.
TF	Temporal Factor.
TFR	Time-Frequency Representation.
tPCA	Temporal Principal Component Analysis.
USA	United States of America.
USC	Universidade de Santiago de Compostela.
VEOG	Vertical Electrooculogram.
VLPFC	Ventrolateral Prefrontal Cortex.
vs	Versus.
WAIS	Wechsler Adults Intelligence Scale
WM	Working Memory.
Y	Young.

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Table of Contents

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

1. Introduction 1

1.1 Visuospatial Working Memory 5

1.2 EEG recording and analyses 9

1.3 Visuospatial working memory and EEG analyses 11

1.4 The impact of aging on visuospatial working memory 15

2. Research aims & Methods 21

2.1 Research aims 23

2.2 Methods 24

2.2.1 Delayed match to sample task 24

2.2.2 Sample characteristics 27

3. Experimental studies 29

3.1 Study 1 31

3.2 Study 2 35

3.3 Study 3 39

3.4 Study 4 69

3.5 Study 5 97

4. General Discussion 103

4.1 Time course of brain activity during encoding and retrieval in visuospatial working memory 105

4.2 Memory load and maintenance duration effects on brain electrical activity supporting visuospatial working memory 106

4.2.1 Memory load effects 106

4.2.2 Maintenance duration effects 108

4.3 Brain oscillatory dynamics and their modulation by memory load during the maintenance of visuospatial information in working memory 109

4.4. Impact of aging on brain activity during encoding and retrieval of information in visuospatial working memory 111

4.4.1 Effects on behavioral performance 111

4.4.2 Effects on ERP components latency 111

4.4.3 Effects on ERP components amplitude 113

4.5 Impact of aging on brain oscillatory dynamics during the maintenance of visuospatial information in working memory 114

5. Conclusions 117

6. Future studies 121

7. References 125

Appendix **159**
Resumo 161

1. Introduction

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

Interest in aging-related topics has experienced a boom in the last few decades in many research fields. Among the many factors that have driven this increase in researchers' interest, the growing proportion of world population aged 65 years old or more stands out (Fig. 1A). Analyses of the Eurostat (at October 2014), the statistical office of the European Union (EU), predicted that this phenomenon will maintain such tendency in the next few decades in developed as well as developing countries. In our nearest environment, reports by Eurostat and the Spanish *"Instituto Nacional de Estadística"* (INE) indicate that the figures for the European Union and Spain are comparable to the predicted world population scenario already at present (Fig. 1B). Moreover, focusing in Galicia, the proportion of old adults is even greater, with a fourth of its population aged over 64 years old. In addition, both agencies prospects also point to a rise in the elderly dependency ratio. That is, the proportion of adults that have reached the legal age for retirement (i.e. 65 years old or more) in relation to those in their working life (i.e. between 16 and 64 years old) is growing steeply and will keep on rising in the near future (Fig. 1B).

These increases in the relative proportions and total numbers of old adults are the result of the great improvements in hygiene and health care, along with changes in living conditions and styles that have occurred in the 19th and 20th century and that are continuing today (for further discussion see Harper, 2014). Nonetheless, human healthy aging still involves a series of cumulative, universal, progressive, intrinsic and deleterious functional and structural changes that usually affect an individual's biological, cognitive, personal, organizational and societal levels (Arking, 2006; Kooij, de Lange, Jansen, & Dikkers, 2008).

Consequently, it is of paramount importance from both an economic and a humanitarian standpoint that older adults remain highly functioning and able to maintain productive and independent lifestyles. Nevertheless, despite some advances have been made in such endeavor, it has been suggested that even if a person maintains good physical and mental health, these does not appear to significantly retard cognitive aging (Posner, 1995). As a result, a remaining crucial challenge to achieve the desired goal of a graceful aging is to promote and ensure an improvement in mental health practices that enable the maintenance of cognitive integrity in old age. Undoubtedly, efforts in this direction would greatly benefit from a better understanding of age-related changes in cognition and from a detailed characterization of cognitive aging.

In this regard, cognitive aging is characterized by a generalized decline in a wide variety of capacities (for review see Glisky, 2007; Park et al., 2002; Sander, Lindenberger, & Werkle-Bergner, 2012). Thus, although verbal knowledge and vocabulary measures tend to increase across the complete lifespan, visuospatial working, short-term and long-term memories as well as processing speed have been found to decline regularly and continuously from the early twenties until death (Park et al., 2002). Moreover, visuospatial abilities have been reported to be further and prominently disrupted in pathological aging

conditions such as mild cognitive impairment and Alzheimer disease (Iachini, Iavarone, Senese, Ruotolo, & Ruggiero, 2009). Remarkably, information and measurements about visuospatial abilities in Parkinson's disease patients have also been demonstrated to be a marker of quality of life in such population (Davidsdottir, Cronin-Golomb, & Lee, 2005).

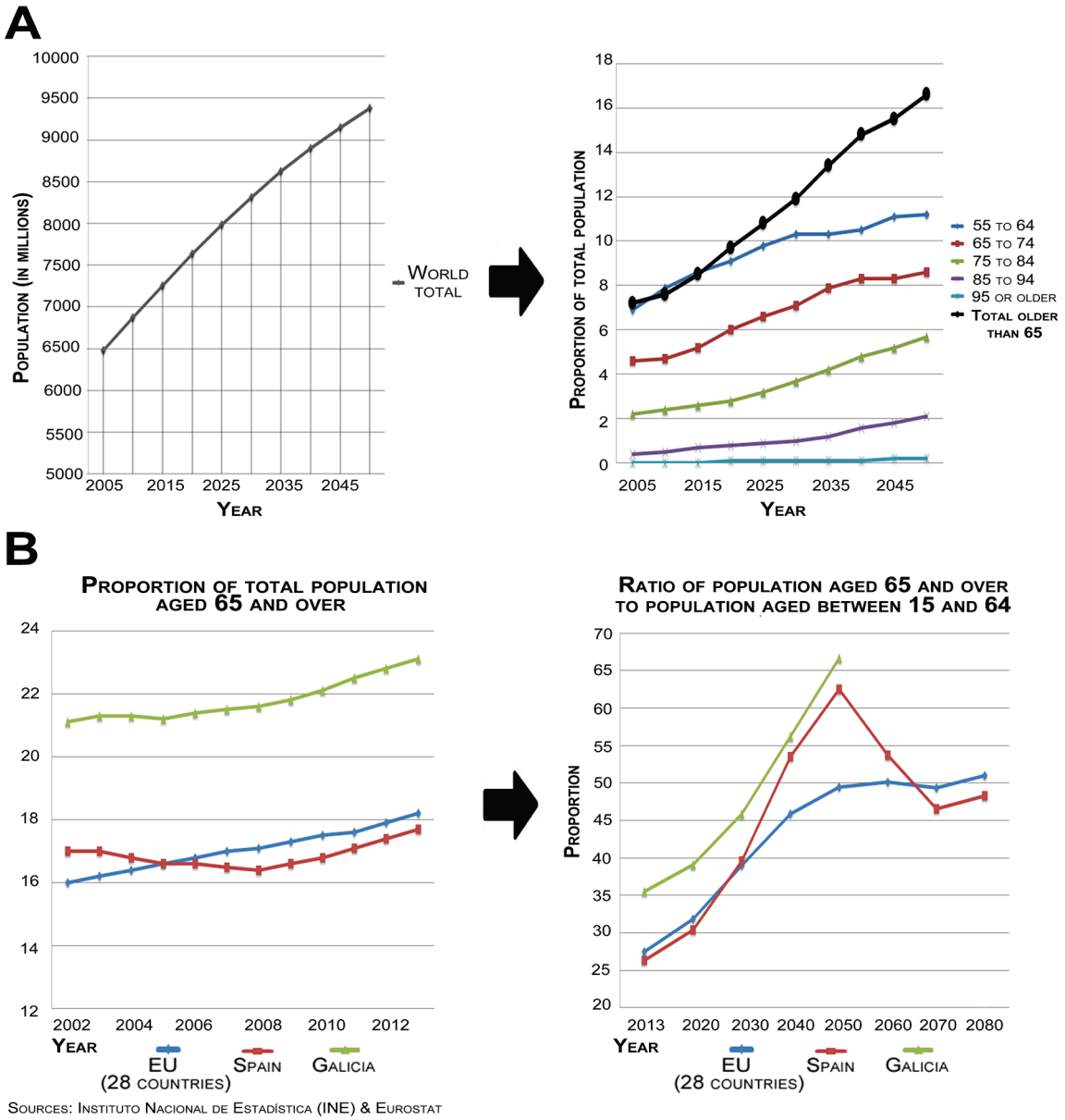


Figure 1. Demographic data. A) Projection of world's population growth from 2005 to 2050 (left) and expected proportion of population aged 55 or more years old in 10 years wide bins for the same time period (right). B) Proportion of population aged 65 and over in the European Union (EU), Spain and Galicia from 2002 to 2013 (left) and projection of the ratio of this population to population between 15 and 64 years old from 2013 to 2080 (right). Note there is no data for Galicia from 2060 onwards.

These findings prompt to a thorough assessment of the basic aspects as well as the evolution along the lifespan of visuospatial abilities, as they seem to be especially sensitive to age-related downturns and partly determine quality of life in some pathological conditions. In addition, working memory is thought to support high level cognitive abilities and to underpin many daily life activities (Baddeley, 2003; Conway, Jarrold, Kane,

Miyake, & Towse, 2007; Hollingworth, Richard, & Luck, 2008; Shah & Miyake, 1999). Thus, the study of visuospatial working memory may be seen as a cornerstone if the final goal of research efforts is to promote independent and high quality life in old adults.

1.1 VISUOSPATIAL WORKING MEMORY

It is worth mentioning here that although short-term (STM) and working memory (WM) have been previously considered independent systems, both terms are being used virtually indistinguishably over the last years. This seems to stem from the lack of an unequivocally accepted distinction between both concepts (Cowan, 2008). Authors in favor of distinguishing both types of memory systems restricted STM to information maintenance processes exclusively, while ascribing manipulation processes operating on stored information to WM (see Baddeley, 2012). In contrast, the main reason for using indistinctly both terms is that most theoretical models of working memory also contain mechanisms for the short-term storage of information (Baddeley & Hitch, 1974; Cowan, 1999; Jonides et al., 2008). It seems, therefore, that this tentative distinction is a matter of the degree of manipulation that a certain task demands on the stored information. Thus, in the present work both terms are going to be used interchangeably, although with a certain preference for working memory as it appears to be a broader concept.

In consequence, visuospatial working memory could be referred as the ability to hold in mind and/or manipulate during brief periods of time small amounts of visuospatial information that are no longer available in the environment (Baddeley, 1998, 2003; Cowan, 1999). This cognitive capacity is thought to comprise three different cognitive events; namely information encoding into memory traces, active maintenance of the memory traces, and retrieval of information from the memory traces for its use, for example, in the recognition of previously encountered information (Jonides et al., 2008).

Among the many different tasks that have been used to study visuospatial WM, delayed match to sample (DMS) (John, Easton, Isenhart, Allen, & Gulyashar, 1996) and Sternberg tasks (Sternberg, 1966) raise as the main two paradigms that enable the assessment of encoding, active maintenance and retrieval operations independently of each other. That is, any of these cognitive events can be studied in isolation thanks to the structure and design of both paradigms. For instance, as illustrated in Figure 2, DMS tasks comprise three different stages that correspond to the three different cognitive events included in WM functioning (Busch & Herrmann, 2003; John et al., 1996; Phillips & Baddeley, 1971; Phillips, 1974). That is, in the first task stage one or several items are presented (simultaneously or sequentially) to the participant, who has to encode this information in WM (encoding). The second task stage is a relatively brief delay period of several seconds, in which the participant should actively held in mind the previously encoded information (maintenance). The final third task stage requires the participant to retrieve the information stored in memory during the first task stage in order to make a

comparison judgment (e.g. presence vs absence or same vs different) between the previously presented item(s) and a probe item or array of items, which is presented in this stage (retrieval/recognition).

Regarding Sternberg tasks, they can be considered a special type of DMS tasks that usually employs digits as memory items and limits the number of stimuli presented during the retrieval stage to only one digit. In this paradigm, the participants are asked to indicate if the digit presented during the retrieval (test or probe stimulus) was on the array presented during the encoding stage (sample stimulus).

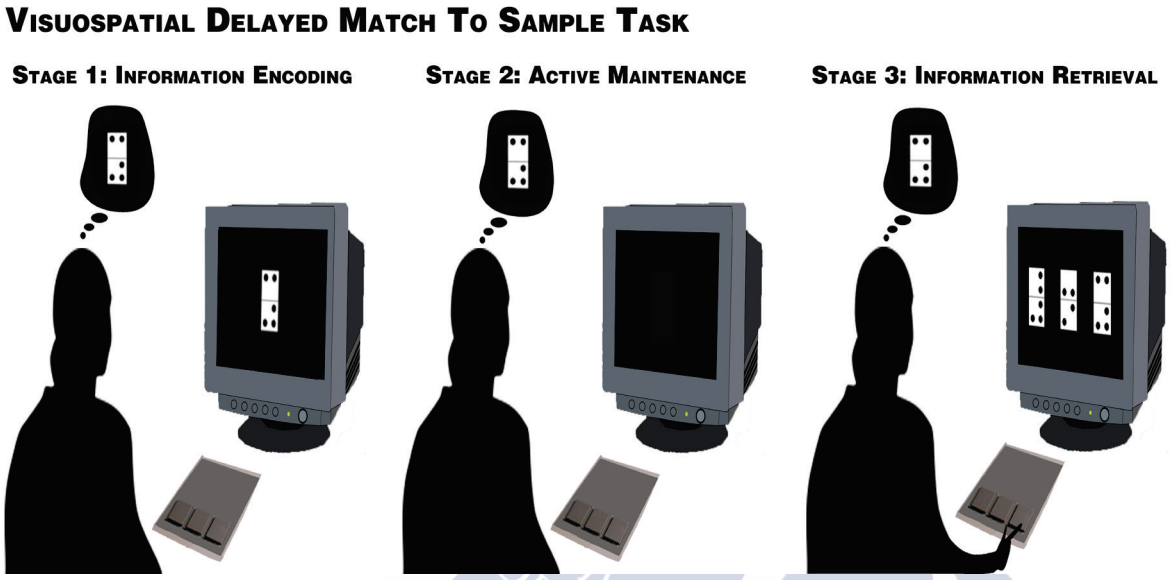


Figure 2. Schematic representation of a trial in a delayed match to sample task. This kind of task includes a first stage in which a memory trace of the visuospatial information presented in the screen is created, followed by a maintenance period along which the memory trace have to be actively held in mind in the absence of stimulation. Finally, an array of new visuospatial items is presented and information must be retrieved from the memory trace in order to execute a comparison between the memory trace information and the new presented items. In the example, this comparison involves the recognition of the first stimulus among those presented in this final stage.

Furthermore, DMS tasks also enable the experimental manipulation of memory load and maintenance duration, which are considered the two main factors limiting WM capacity. In the one hand, memory load, which is determined by the amount and complexity of the items to be held in mind, could be manipulated by changing in a trial to trial basis the number and/or visuospatial complexity of the items presented during the first task stage. When memory load is manipulated, poorer performance in the experimental tasks has been usually observed under high levels of memory load than under low levels (Alvarez & Cavanagh, 2004; Awh, Barton, & Vogel, 2007; Bays & Husain, 2008; Eng, Chen, & Jiang, 2005; Luck & Vogel, 1997; Zhang & Luck, 2008). Competition for a limited pool of processing resources (Bays & Husain, 2008) and/or for a limited number of available memory slots (Delvenne & Bruyer, 2004; Zhang & Luck, 2008) seem to be the reasons behind this memory load dependent effect on WM function. The latter hypothesis implicates that there is a fixed limit in the capacity of WM, which is determined by the

number of items and/or features of an item to be retained, independently of their resolution. In contrast, the former hypothesis suggests that this WM capacity limit is variable depending on the resolution of the mnemonic representations. Thus, storage of large amounts of items will be possible albeit with lower resolution per object than conditions in which fewer items are maintained in WM. Probably, differences in task demands determine if resolution is a determinant factor for WM capacity (see Delvenne and Bruyer, 2004; Zimmer, 2008).

On the other hand, maintenance duration refers to the temporal extension of the information maintenance period, which spans from information encoding to retrieval. Accordingly, the use of different time delays between the encoding and the retrieval stage is a suitable way to experimentally manipulate this factor. Studies using such manipulation have found that increases in the duration of the maintenance period worsen task performance (Cornelissen & Greenlee, 2000; Gold, Murray, Sekuler, Bennett, & Sekuler, 2005; Phillips & Baddeley, 1971; Phillips, 1974; van der Ham, van Wezel, Oleksiak, & Postma, 2007). Time-based decay theories points to a progressive weaken of memory traces due to the mere passage of time. Such decrease in memory traces' fidelity could be related to the stochastic variability that is inherent to neuronal firing and synchrony, which potentially causes the neurons making up a representation to gradually fall out of synchrony and consequently, blurs the memory traces with noise (for a detailed discussion see Jonides et al., 2008).

This last explanation refers to some aspects of the neurobiological underpinnings of WM. Regarding this topic, working memory has been a major topic of research in neurosciences for nearly 50 years now. The traditional approach on neuroscience has focused on investigating neurocognitive function based on attempts to localize processes in space (i.e., functional localization) (M. X. Cohen, 2011). This has been a useful approach and was critical for the development of cognitive neuroscience theories, experiments, and statistical measures. Indeed, it has been recently considered that different brain regions has specific functions, which are coordinated in transient process-specific alliances depending on task demands and individual goals (Cabeza & Moscovitch, 2013; Zimmer, 2008). In this way, visuospatial WM is thought to emerge from the coordinated activity of brain regions extending from frontal to parietal and temporal cortices (J. D. Cohen et al., 1997; D'Esposito, Postle, & Rypma, 2000; Hartley & Speer, 2000; Linden, 2007; Petrides, 2000; Smith & Jonides, 1999) (Figure 3).

Within this fronto-parietal network, the initial sensory processing and the storage of object representations are carried out in the so-called ventral and dorsal streams (Baddeley, 2003; Müller & Knight, 2006; Passaro et al., 2013; Todd & Marois, 2004; Xu & Chun, 2006). The former, which deals with physical aspects of visual information, starts in inferior areas of the visual cortex and ends in the inferior temporal gyrus (passing by the fusiform and lingual gyri); while the latter, which handles spatial aspects of information,

also begins in visual cortex but continues dorsally to the inferior and superior parietal cortices (in the vicinity of the intraparietal sulcus) (Ungerleider & Haxby, 1994). Further, both streams follow a pattern of increasing abstraction of the object representation from the visual cortex to the endpoint of each stream. In addition, structures in the medial temporal lobe such as the perirhinal and entorhinal cortices, as well as the hippocampus and parahippocampal gyrus may also aid in the storage and rehearsal of some kinds of novel information (Passaro et al., 2013; Ranganath, 2006; Zimmer, 2008).

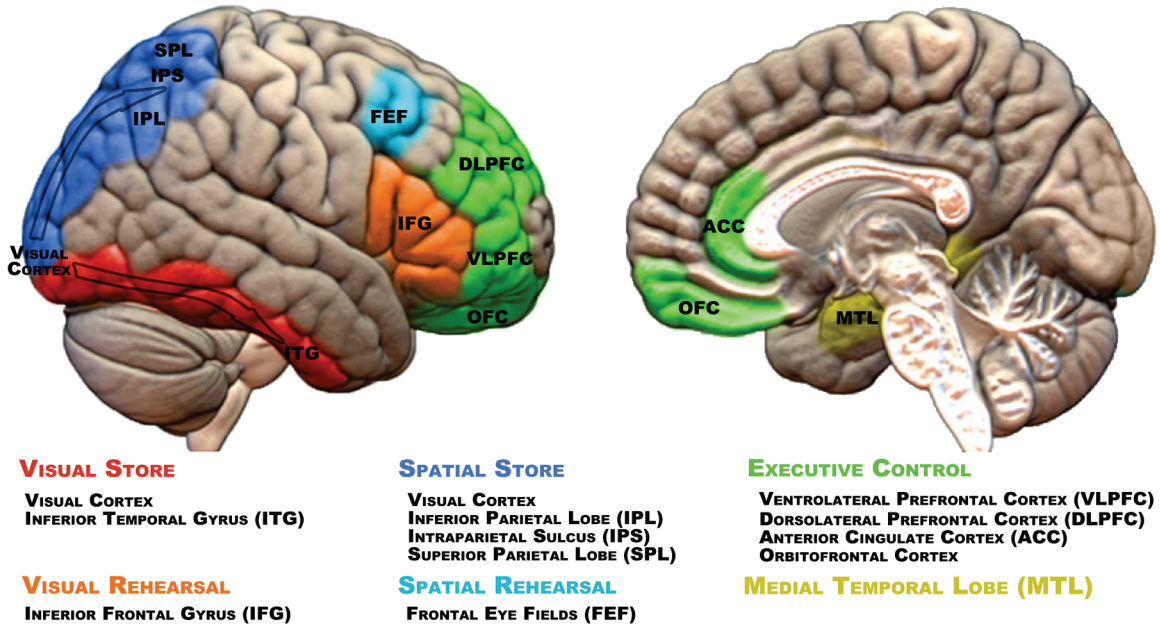


Figure 3. Schematic representation of the fronto-parietal network supporting WM. Initial processing and storage of visual and spatial information is split in a dorsal stream (dark blue) encompassing from occipital to parietal cortices, and a ventral stream (red) extending from occipital to temporal regions. These streams would store spatial and visual aspects of information, respectively. Regarding, rehearsal of stored representations, it would be handled by frontal structures. In particular, those colored in light blue support spatial rehearsal and those marked in orange, rehearsal of visual aspects of stored representations. Finally, executive control processes would be mainly carried out by the frontal and prefrontal regions highlighted in light green.

As regards frontal regions, they seem to support rehearsal as well as executive control processes (Corbetta & Shulman, 2002; Kane & Engle, 2002; Kessels, Postma, Wijnalda, & de Haan, 2000; Postle & D'Esposito, 1999; Postle, Druzgal, & D'Esposito, 2003). In particular, inferior and superior frontal gyri (especially, the frontal eye fields) help rehearsal of stored materials. Interestingly, these regions also seem to be sensitive to the modality of the representation. Thus; the inferior frontal gyrus may help rehearsal of visual representations whereas the superior frontal gyrus serves rehearsal of spatial representations. Regarding the executive control over posterior processing of information, it may be exerted by the lateral prefrontal cortex and parts of orbitofrontal and anterior cingulate cortices. In contrast to more posterior regions, lateral prefrontal cortex is probably split depending on the nature of the process being carried out but not on the modality of the representations. In this way, ventral areas are thought to control different

aspects that help active maintenance of information representations and their continuous reactivation, while dorsal areas probably accomplish any kind of manipulation of information representations, exerting an active form of executive control (D'Esposito, Postle, Ballard, & Lease, 1999; Owen, 1997; Ranganath, 2006).

However, information processing in the brain is a complex matter and, thus, many aspects of this cognitive capacity remain elusive for this traditional neuroscience approach. For instance, recent reviews of WM research have highlighted the lack of a thorough knowledge about the timing and the temporal course of brain activity supporting information encoding, maintenance and retrieval (Baddeley, 2012; Jonides et al., 2008). In fact, the importance of timing is underlined by the fact that functional communication and coordination of brain regions forming process-specific transient alliances within the aforementioned fronto-parietal network, are supposed to be carried out through heightened and synchronized patterns of neuronal firing (Buzsáki & Draguhn, 2004; Buzsáki, 2006; Jonides et al., 2008; Zimmer, 2008). Moreover, this neuronal synchronization in different frequency bands has been also demonstrated to play an important role in the maintenance of representations in WM as well as in the neurophysiological mechanisms determining the capacity limits of WM (Raffone & Wolters, 2001; Roux & Uhlhaas, 2014; Vogel, Woodman, & Luck, 2001; Werkle-Bergner, Müller, Li, & Lindenberger, 2006).

Therefore, research that enables the assessment of synchronization between neuronal assemblies as well as the study of brain activity with a fine temporal resolution should be a helpful source to shed light in those elusive topics about brain function underlying visuospatial WM. Accordingly, research analyzing electroencephalographic (EEG) recordings, which provides a continuous measure of brain activity with a temporal resolution of milliseconds, might provide valuable insights in such topics.

1.2 EEG RECORDING AND ANALYSES

Electroencephalographic recordings are a non-invasive technique that enables direct registering of biophysical phenomena at the level of populations of neurons. Note, however, that it is not yet possible to know which exact neurophysiological factors contribute in what proportion to EEG signals recorded at the scalp, since they are a combination of several of these factors (M. X. Cohen, 2014). Furthermore, EEG signals provide a continuous measure of neural processing. Consequently, any modulation on this processing due to specific experimental manipulations allow researchers to determine relations and draw associations between certain stages of information processing and the underlying neural events (M. X. Cohen, 2014; Luck, 2005). As a result, this technique has a more straightforward relationship with neural activity than functional Magnetic Resonance Imaging (fMRI) measures that depend on the hemodynamic response, such as Blood-Oxygen Level Dependent (BOLD) (M. X. Cohen, 2014; Luck, 2012). Also, EEG recordings have a temporal resolution in the order of milliseconds. Accordingly, EEG has a

finer temporal resolution than fMRI and Positron Emission Tomography (PET) recordings, since the latter techniques rely in the sluggish nature of the hemodynamic response. Nevertheless, fMRI and PET have a more precise spatial resolution than EEG techniques, and, therefore, EEG based analysis techniques are better suited than classic neuroimaging techniques to capture fast, dynamic and temporally sequenced cognitive processes.

Other advantage of EEG recordings is that they can be repeatedly and safely applied to the same individuals, and, consequently, they are widely used (Rossini et al., 2006). Moreover, compared with classic neuroimaging techniques like fMRI or PET, and even with Magnetoencephalographic (MEG) recordings, EEG recordings are inexpensive and simple to apply (Luck, 2005). This enables an easy transfer of EEG-based techniques from research laboratories to clinical settings.

Besides these advantages, EEG is a powerful tool to assess brain activity because of its multidimensionality (M. X. Cohen, 2014). In fact EEG signals can be explored at least in four dimensions: time, space, frequency and power and phase. In order to examine these dimensions there are two major approaches, namely the analysis of event-related potentials (ERPs), which assess changes of voltage over time and space (measured through different electrodes), and the analysis of oscillatory activity, which enables the examination of all four dimension, albeit with lower precision than ERPs in the time domain.

The ERP originates from the summation of postsynaptic potentials that occurred at the same time in similarly oriented neurons (likely, in dendrites of pyramidal cells) in a way that constitute a stereotyped electrophysiological response to a specific internal or external event. Therefore, an ERP is a waveform composed by a series of positive and negative deflections of voltage, which are considered components and which reflect aspects of brain activity that have a (relatively) stable time relationship with a definable reference event, such as the presentation of a stimulus, the preparation or execution of a motor response, etc. (Luck, 2005, 2012). Two main parameters of the ERP components are usually analyzed: i) their amplitude, which quantifies the change in voltage with respect to a baseline period at any given point in time for any recorded electrode; and ii) their latency, defined as the time elapsed since the reference event to the point of measurement, which usually coincides with an inflection in the waveform (thus, with the beginning, peak or end of a certain component).

As regards oscillatory activity, it registers rhythmic changes or fluctuations in the excitability of populations of neurons. Like in the case of ERPs, such fluctuations also stem from the summation of excitatory or inhibitory postsynaptic potentials in similarly oriented neurons (Sauseng & Klimesch, 2008). Accordingly, oscillations are thought to reflect a mechanism that facilitates the formation of coherently organized groups of neurons via the establishment of transient temporal correlations (J. M. Palva, Monto, Kulashekhar, & Palva, 2010; Roux & Uhlhaas, 2014; Varela, Lachaux, Rodriguez, & Martinerie, 2001). Also, given that brain circuits of different size show different resonance

properties, it is likely that brain rhythms of different frequency can dissociate specific brain networks and index different functional roles (Sauseng & Klimesch, 2008; von Stein & Sarnthein, 2000). At a practical level, any oscillation can be represented as a sine wave and described and analyzed by various parameters: i) its frequency, which refers to the oscillatory speed, and is usually expressed as the number of complete cycles within the sine wave per unit of time (usually, a second); ii) its amplitude or power, both measures reflect the magnitude of brain electrical activity in a given frequency band (power is the squared amplitude); and iii) its phase, which represents the position along the sine wave at any given time point (commonly expressed in degrees, between 0º and 360º).

Furthermore, using either ERPs or oscillatory activity, there are common ways to study EEG signals' spatial dimension. That is, the distribution of the signal at the scalp could be analyzed when it is recorded with a sufficient number of electrodes. Similarly, the estimation of source activity depends on the numbers of electrodes, too. Thus, when a large number of electrodes is used, this facilitates the application of some algorithms (e.g. weighted minimum norm, beamformer, moving dipoles, low resolution electromagnetic tomography,…) designed to solve the inverse problem and estimate the activity of the brain sources for the signal recorded at the scalp. These estimations, however, possess a rather poor spatial resolution as compared with classic neuroimaging techniques (for review see Grech et al., 2008; Yao & Dewald, 2005).

1.3 VISUOSPATIAL WORKING MEMORY AND EEG ANALYSES

Multiple studies have combined the use of EEG recordings and WM tasks to assess different aspects of visuospatial WM. As a result, several different components of the ERPs have been considered a correlate of the cognitive processes needed for the successful encoding, maintenance and retrieval of information. Similarly, oscillatory activity in different frequency bands is supposed to index several aspects of information processing in the brain during working memory operations.

As concerns ERP components, early deflections like P1 or N1, which have latencies shorter than 200 ms, are thought to reflect perceptual processing in the visual cortex (Luck, Heinze, Mangun, & Hillyard, 1990; Schendan & Lucia, 2010). Indeed, these components have been localized to the extrastriate cortex and posterior temporal areas (e.g. lingual and fusiform gyri) (Di Russo, Martinez, Sereno, Pitzalis, & Hillyard, 2001; Fort, Besle, Giard, & Pernier, 2005). Nevertheless, they are also sensitive to top-down modulation (Clark & Hillyard, 1996; van Elk, van Schie, Neggers, & Bekkering, 2010; Vogel & Luck, 2000). In addition, P2 and N2 components are considered indexes of stimulus evaluation, dealing with the detection of task relevant features (Luck & Hillyard, 1994; Potts, 2004) and general aspects of monitoring and evaluation of a stimulus (Folstein & van Petten, 2008), respectively. Moreover, both components are supposed to receive contributions from neural activity in the frontal cortex, particularly from orbitofrontal and anterior cingulate

cortices (Bokura, Yamaguchi, & Kobayashi, 2001; Potts & Tucker, 2001). Another endogenous component, P300, has been traditionally related to stimulus categorization (Azizian, Freitas, Watson, & Squires, 2006; Donchin, 1981; Johnson Jr & Donchin, 1980; Kok, 2001; Magliero, Bashore, Coles, & Donchin, 1984; Mecklinger & Ullsperger, 1993; Nasman & Rosenfeld, 1990; Polich, 2003). This component seems to arise from the combination of activation in several brain regions in frontal, temporal and parietal cortices as well as other structures such as hippocampus or thalamus (Baudena, Halgren, Heit, & Clarke, 1995; Bledowski et al., 2004; Halgren et al., 1980, 1995; McCarthy, Wood, Williamson, & Spencer, 1989; Mecklinger & Ullsperger, 1995; Soltani & Knight, 2000; Verleger, Heide, Butt, & Kömpf, 1994; Yamazaki et al., 2000; Yamazaki, Kamijo, Kiyuna, Takaki, & Kuroiwa, 2001; Yingling & Hosobuchi, 1984).

These ERP components have been observed in different DMS tasks designed to assess specific aspects of WM function. However, to the best of our knowledge, there have not been any attempts to integrate all these ERP components and the processes they reflect in order to cast light on the temporal course of brain activity supporting information encoding and retrieval in WM. Consequently, despite knowledge about specific aspects of brain activity underpinning WM function is growing, there is a lack of a thorough and detailed knowledge about the temporal dynamics of neural processing (see Baddeley, 2012; Jonides et al., 2008).

To fill the abovementioned knowledge gap, the study of ERP with complex but objective analysis techniques like principal component analysis (PCA) would be of great interest (Picton et al., 2000). This kind of analysis increases the possibility of describing features of the brain activity time course more objectively and accurately than is possible with the unaided eye. That is, PCA is used to detect features of the ERP waveform that might escape visual inspection due to ERP components overlap and summation (Dien, Beal, & Berg, 2005; Dien & Frishkoff, 2005; Dien, 1998). Its main advantage is that it presents each ERP component with its "clean" shape, extracting and quantifying them free from the influences of adjacent or subjacent components (while traditional grand averages can yield a distorted view of components or may even not show some of them) (see Luck, 2005). Thus, applying a temporal PCA on a recorded ERP (i.e. on its voltage values along the time axis) would result in a series of latent factors representing the main constituents of its time course, i.e. the ERP components that comprise objectively and significantly the information processing time course.

Besides this, previous studies reported that several of the aforementioned ERP components are sensitive to memory load and maintenance duration manipulations in DMS tasks (Morgan, Klein, Boehm, Shapiro, & Linden, 2008; Soria Bauser, Mayer, Daum, & Suchan, 2011; van der Ham, van Strien, Oleksiak, van Wezel, & Postma, 2010). Regarding the latter, however, only effects on N2 component during WM retrieval have been reported (van der Ham et al., 2010). Therefore, it remains unclear if maintenance duration

manipulations modulate other stages or cognitive processes during visuospatial WM retrieval.

With respect to memory load, previous reports indicate that P1, N1 and P300 showed different modulations of their amplitude and latency depending on the cognitive process that was evaluated, i.e. depending if the ERP was analyzed during encoding or during retrieval (Houlihan, Stelmack, & Campbell, 1998; Morgan et al., 2008; Soria Bauser et al., 2011; Studer et al., 2010). For instance, larger P1 and N1 amplitudes have been observed during WM encoding under high than low load conditions in a previous study with a DMS task (Morgan et al., 2008). However, a latter study with a similar task did not find such modulations (Soria Bauser et al., 2011). Further, while both studies reported lower N1 amplitudes in high than low load conditions during retrieval, they differ on P1 amplitude modulation by memory load during this stage. Likewise, during the encoding stage of DMS tasks several studies found larger P300 amplitudes with higher memory load levels (Houlihan et al., 1998; Studer et al., 2010), whereas other studies informed of the opposite effect (Morgan et al., 2008; Soria Bauser et al., 2011). Memory load dependent P300 amplitude modulations during WM retrieval in these studies were also partly opposed. Accordingly, how visuospatial WM load modulations affect these ERP components during encoding and retrieval of information remains a matter of debate.

In consequence, **Study** 1, described in section 3.1, will focus on brain activity during visuospatial WM encoding and retrieval processes. In particular, this study will describe a newly designed visuospatial DMS task that uses adapted domino tiles as stimuli. Importantly, the use of domino tiles was decided because they comprise a variable number of dots arranged in various spatial configurations. This DMS task is adapted to EEG recordings, which allowed analyzing the ERPs corresponding to information encoding and retrieval stages. Such analysis was done through temporal PCA, which decompose the ERP waveform in one or more factors that explain its variance in time, thus corresponding to the different temporal links in the information processing chain. Moreover, **Study 1** will also tackle some aspects related to the capacity limits of WM during information encoding and retrieval. To that end, maintenance duration was manipulated by interposing two different time lengths between encoding and retrieval whereas memory load was varied by changing the number of dots within a domino tile. These manipulations enable the assessment of memory load dependent effects on ERP components during WM encoding and retrieval, as well as maintenance duration dependent effects during WM retrieval.

Turning to oscillatory activity, different frequency bands have been associated with processes that can be considered building blocks of WM function. For instance, fast oscillatory activity in beta (13-30 Hz) and gamma (>30 Hz) bands has been considered an index of neuronal firing in neural assemblies, thus being a correlate of the maintenance of representations in WM (S. Palva, Kulashekhar, Hämäläinen, & Palva, 2011; Tallon-Baudry, Kreiter, & Bertrand, 1999). Slower rhythms, such as theta (4-7 Hz) or alpha (8-12

Hz) has been related to executive control processes (Buzsáki, 2006; Freunberger, Werkle-Bergner, Griesmayr, Lindenberger, & Klimesch, 2011; Sauseng et al., 2009).

In addition, all these rhythms has been shown to be modulated by memory load during the maintenance of information in WM (S. Palva et al., 2011). Nonetheless, different studies have reported conflicting results regarding such memory load dependent modulations, especially, for alpha band activity. That is, during the maintenance period of a wide variety of WM tasks, both increases (Busch & Herrmann, 2003; N. R. Cooper, Croft, Dominey, Burgess, & Gruzelier, 2003; Jensen, Gelfand, Kounios, & Lisman, 2002; Schack & Klimesch, 2002; Scheeringa et al., 2009; Tuladhar et al., 2007) and decreases (Gevins, Smith, McEvoy, & Yu, 1997; Gundel & Wilson, 1992; Stipacek, Grabner, Neuper, Fink, & Neubauer, 2003) dependent of memory load were observed in alpha power and synchrony at posterior cortical regions.

This diversity in memory load modulations of alpha activity is probably due to the fact that these oscillations are produced by different mechanisms depending on the level of the generating region within the visual processing stream hierarchy (Bollimunta, Chen, Schroeder, & Ding, 2008). Indeed, studies with non-human primates indicate that information processing may be facilitated by alpha activity increases in inferior temporal cortices and decreases in occipital regions (Bollimunta et al., 2008; Mo, Schroeder, & Ding, 2011). Similarly, studies in human participants have reported that both phenomena (i.e. increases and decreases of alpha power) are not mutually exclusive as they can be obtained on different alpha sub-bands and cortical regions (Grimault et al., 2009; Meltzer et al., 2008; Michels et al., 2010; Michels, Moazami-Goudarzi, Jeanmonod, & Sarnthein, 2008; Sauseng, Klimesch, Doppelmayr, et al., 2005).

Interestingly, some of the studies that observed concurrent increases and decreases of alpha activity, reported memory load dependent increases of alpha activity in frontal cortical sites (Grimault et al., 2009; Michels et al., 2010; Sauseng, Klimesch, Doppelmayr, et al., 2005). Such concurrent modulations have been interpreted as a posterior alpha activity modulation by alpha signals from frontal regions, which reflect a top-down control mechanism. Indeed, there are other examples of memory load dependent increases in frontal alpha power and fronto-parietal coupling of alpha activity (Leiberg, Lutzenberger, & Kaiser, 2006; J. M. Palva et al., 2010; S. Palva et al., 2011; Sauseng, Klimesch, Schabus, & Doppelmayr, 2005; von Stein & Sarnthein, 2000).

Given that alpha activity has been consistently related to active inhibition (Jensen & Mazaheri, 2010; Klimesch, Sauseng, & Hanslmayr, 2007; Pfurtscheller, Stancák, & Neuper, 1996), these findings raise the possibility that alpha oscillatory dynamics contribute to WM function in several ways, specifically: (i) by strengthening maintenance of stimulus representations through alpha decreases in posterior task-relevant regions; (ii) by suppressing distractor information through alpha increases in posterior task-irrelevant regions; and (iii) by sending top–down control signals from different regions within

prefrontal cortex (PFC) to posterior cortices, as reflected by increases in frontal alpha activity and fronto-parietal coupling. However, such possibility has not been tested so far.

Accordingly, **Study 2**, which is presented in section 3.2, will address the dynamics of brain activity during information maintenance in a visuospatial WM DMS task. For that purpose, oscillatory activity during the delay between the sample stimulus and the probe stimulus has been analyzed. Special interest was focused on alpha band activity; on testing whether different dynamics of alpha activity could coexist and which role they may play in visuospatial WM maintenance. Further, the effects of memory load in these alpha dynamics were also carefully evaluated.

1.4 THE IMPACT OF AGING ON VISUOSPATIAL WORKING MEMORY

Neuroscientific and psychological research has long been used to assess the impact of aging on cognitive capacities. As already mentioned in the first section of the introduction, experimental data suggest that old adults are characterized by a generalized decline of their cognitive capacities when compared with young adults (Baltes, 1993; Fournet et al., 2012; Glisky, 2007; Park et al., 2002; Park, Polk, Mikels, Taylor, & Marshuetz, 2001; Rönnlund, Nyberg, Bäckman, & Nilsson, 2005). Visuospatial working memory is, evidently, among these cognitive capacities (Fournet et al., 2012; Glisky, 2007; Hale et al., 2011; Kessels, Meulenbroek, Fernandez, & Olde Rikkert, 2010; Park et al., 2002). These declines are not only reflected in lower accuracy rates (and higher error rates) and longer reaction times in the experimental tasks, but also on a lower span or capacity of WM and on reduced resolution of the visuospatial mnemonic representations (Noack, Lövdén, & Lindenberger, 2012; Peich, Husain, & Bays, 2013). Further, these declines seem to be especially severe in the visuospatial domain as compared with other domains (e.g. the verbal domain) (Hale et al., 2011; Park et al., 2002) and boosted under high cognitive demands (Gazzaley, Sheridan, Cooney, & D'Esposito, 2007; Kessels et al., 2010). The latter, led some authors to suggest that old adults are more sensitive to cognitive demand than young adults (Cabeza & Dennis, 2013; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008).

Different hypotheses have been put forward in order to explain these age-related declines in WM function. Among them, one of the most influential has suggested that a generalized slowing of processing speed can account for a wide part of the evidence on age-related declines (Rousselet et al., 2009, 2010; Salthouse, 1996, 2000). This hypothesis was initially based on experimental results showing longer reaction or execution times in old than young adults in a wide variety of tasks. Therefore, despite its scope extends beyond WM, it also encompasses WM processing. In short, it suggests that cognitive processes may be disrupted by two consequences of a slower speed of information processing. First, it is possible that a cognitive operation or task have to be executed in a limited time window (limited time principle). Therefore, if early steps in this cognitive operation occupied a significant proportion of the available time, then latter processes

would not have enough time to be successfully completed; alternatively it is also possible that the adequate time window for a certain process ends before it is completed. Second, it is possible that some neural processing requires the synchronization of different sub-processes, or that certain processes need the output of some previous processing operation (simultaneity principle). Thus, delays in a certain sub-process can ruin the whole processing chain because they produced badly timed outputs or because they lost synchrony with other sub-processes.

Other explicative hypotheses stem from the reduced capacity showed in WM tasks by old adults relative to young adults, (Park, 2000; Salthouse, 1990). Specifically, two factors are supposed to mediate the reduction in WM capacity with age; namely an age-related reduction in processing resources and a deficit in inhibitory processing. As regards the former, processing resources could be considered as a general purpose pool of available mental energy that can be allocated to a small number of concurrent mental activities (Craik & Byrd, 1982; Craik & Rose, 2012), despite there is a lack of a widely accepted definition. Such age-related reduction in mental energy will impede the use of self-initiated strategies as well as disrupt the magnitude and effort that could be allocated to mental processing (Craik & Rose, 2012). Regarding the inhibitory function deficit in old adults (Gazzaley & D'Esposito, 2007; Hasher & Zacks, 1988), the central assumption of this hypothesis, as proposed by Hasher and Zacks (1988), is that under some circumstances (i.e. including aging) the efficiency of executive control in general and inhibitory processes in particular is reduced. Such reduction allows more irrelevant information to enter working memory, thus capturing WM capacity. This fact may then underlie the reduced rates of success in accessing required information from memory and produce poorer performance in WM tasks.

Interestingly, some of these hypotheses made direct allusions at processes or facts that are supposed to be measurable by EEG analysis techniques (e.g. processing time, processing resources ...). Remarkably, brain activity changes due to normal aging has been extensively studied in neurosciences (see Fabiani, 2012; Grady, 2008, 2012; Park et al., 2001; Reuter-Lorenz & Park, 2010; Sander, Lindenberger, et al., 2012), and some attempts have been made to link these changes with findings from behavioral experiments (e.g. Park et al., 2001; Reuter-Lorenz & Park, 2010). In light of results of neuroscience research, some authors have argued that encoding processes concentrate more age-related changes in brain activity than retrieval (Craik & Rose, 2012; Finnigan, O'Connell, Cummins, Broughton, & Robertson, 2011; Friedman, Nessler, & Johnson Jr, 2007; Park et al., 2001). Nevertheless, most ERP research on age-related differences on visuospatial WM function has been carried out with experimental tasks in which the different cognitive events included in WM (i.e. encoding, maintenance and retrieval) cannot be assessed

independently of each other (e.g. n-back tasks[*]). Consequently, whether the age-related changes proposed in the aforementioned hypotheses have a reflection in the ERP components during encoding and during retrieval processes remains a matter of debate.

Notwithstanding, there are a few studies that combined the use of a visuospatial DMS task with ERP analyses. On the one hand, during information encoding in those previous studies, longer P1, N1 and/or P300 latencies were observed in old than young adults (Finnigan et al., 2011; Gazzaley et al., 2008; Zanto, Toy, & Gazzaley, 2010). Hence, results from these studies support the existence of a generalized age-related slowing of processing speed during WM encoding. In contrast, the potential effects of the suggested reductions in WM capacity during information encoding in visuospatial WM has not yet been explicitly assessed, to the best of our knowledge.

Consequently, **Study 3**, which is going to be expounded in section 3.3, will evaluate age-related changes in brain activity during visuospatial information encoding in WM. In particular, it will test whether there is an age-related generalized slowing of processing speed. Furthermore, it will evaluate the interaction of age with memory load effects too, in order to explore possible correlates of a reduction in the allocation of processing resources in old relative to young adults as well as to evaluate whether old adults are more sensitive than young adults to memory load modulations. Finally, trying to integrate brain activity and behavioral changes, **Study 3** will examine the possible correlations between changes in ERP components and accuracy rates or reaction times.

On the other hand, as far as information retrieval and recognition is concerned, the picture is similar to that presented for information encoding. That is, analysis of ERPs in previous studies reported longer N1 and/or P300 latencies in old than young adults during visuospatial information retrieval and recognition (Knott et al., 2004; Müller & Knight, 2002; Pelosi & Blumhardt, 1999; Pratt, Michalewski, Patterson, & Starr, 1989). This is in accordance with a generalized slowing of processing speed in old adults. Additionally, those studies in which the interaction of age-related and memory load dependent effects was analyzed failed to find statistically significant results (Pelosi & Blumhardt, 1999; Pratt et al., 1989). Thus, no evidence in favor of a reduction of WM capacity was collected so far. However, these latter studies employed digits as stimuli, and so, it remains unclear if the aforementioned interactions could appear for complex visuospatial materials. It remains also elusive the possible interaction between age-related and maintenance duration related effects on electrophysiological activity supporting visuospatial information retrieval and recognition in WM.

Resultantly, **Study 4**, which is described in section 3.4, will examine the effects of aging on brain activity supporting visuospatial retrieval and recognition in WM. The

[*] Participants in this task are asked to response every time the presented stimulus in a series of stimulus matched the relevant feature of the stimulus presented "n" times before, i.e. 1-back if it matches the previously presented stimulus, 2-back if it matches the stimulus presented just before the previous one, and so on.

interaction of age-related effects with those of maintenance duration and memory load will also be addressed in search for evidence of a reduced WM capacity in old adults. Additionally, **Study 4** will also study whether age-related slowing of processing speed affects different sub-processes of visuospatial WM recognition.

Finally, as regards information maintenance in WM, the focus turns to oscillatory brain activity. For instance, alpha power was found to be reduced in old relative to young adults in previous studies (Babiloni et al., 2004; McEvoy, Pellouchoud, Smith, & Gevins, 2001; Sander, Werkle-Bergner, & Lindenberger, 2012). Such change in alpha oscillatory activity has further been related to a deficit in inhibitory processes (Babiloni et al., 2004; Sander, Werkle-Bergner, et al., 2012), which is more severe under high memory load conditions (Sander, Werkle-Bergner, et al., 2012). Nevertheless, despite the importance of synchronization of neuronal populations for WM function, the well-known decline of WM functioning in normal aging has not yet been investigated from this perspective. Accordingly, it remains an open question how senescent changes in inhibitory function alter WM-related neural mechanisms and circuitries as revealed by oscillatory synchrony.

Interestingly, recent neuroimaging studies have reported a special case of deficient inhibition in old adults that affects neural networks. That is, some studies have observed a deficit in the balanced activation of functional brain networks in old as compared to young adults (Andrews-Hanna et al., 2007; Park, Polk, Hebrank, & Jenkins, 2010; Sambataro et al., 2010). In particular, these findings refer to the lack of equilibrium between the fronto-parietal network supporting WM function and another functional network called the default mode network (or resting state network). The latter is a set of brain regions that is usually deactivated during task execution relative to resting state periods (Greicius, Krasnow, Reiss, & Menon, 2003; Gusnard & Raichle, 2001; Harrison et al., 2008; Raichle & Snyder, 2007), and thus, it is supposed to mediate mind wandering and self-referential thoughts (Buckner, Andrews-Hanna, & Schacter, 2008; Spreng & Grady, 2010; Spreng, Mar, & Kim, 2009). This default mode network (DMN) has been found to be more active during task execution in old than young adults (Lustig et al., 2003; Park et al., 2010; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007; Sambataro et al., 2010), which, in turn, was associated with poorer performance in WM tasks, especially under high memory load conditions. Nevertheless, the neural mechanism responsible for this DMN over activation and for the inefficient orchestration of these functional networks remains elusive.

Remarkably, results from previous studies have revealed that alpha amplitude and phase modulate gamma activity in small local cortical circuits in the animal (Haegens, Nácher, Luna, Romo, & Jensen, 2011; Spaak, Bonnefond, Maier, Leopold, & Jensen, 2012) and human (Osipova, Hermes, & Jensen, 2008; Yanagisawa et al., 2012) brains. Further, this inter-frequency interaction has been linked with the inhibitory functions of alpha frequency. In this way, alpha cycle could be divided into an excitatory part, where gamma activity is preferentially coupled, and an inhibitory part, where no gamma activity

should be present. This interaction is believed to promote an efficient communication between different neuronal populations. Arguably this phase:amplitude coupling (PAC) between oscillations in alpha and gamma frequencies might be also suitable for long-range communication within functional networks in the brain. Indeed, it has been previously proposed as a neural mechanism implicated in information maintenance in STM (Roux & Uhlhaas, 2014; van der Meij, Kahana, & Maris, 2012; Van Vugt, Chakravarthi, & Lachaux, 2014). In such mechanism, alpha would work as a pulsed inhibitory signal precisely controlling information flow in the brain and cortical activity timing (Jensen, Gips, Bergmann, & Bonnefond, 2014; Klimesch et al., 2007); whereas gamma would reflect synchronous firing in small neuronal assemblies (Crone, Sinai, & Korzeniewska, 2006; Fries, Nikolić, & Singer, 2007), probably representing the maintenance of information representations stored in memory (Freunberger et al., 2007; Jokisch & Jensen, 2007; Kaiser, Heidegger, Wibral, Altmann, & Lutzenberger, 2008; Tallon-Baudry & Bertrand, 1999; Tallon-Baudry et al., 1999; Van Vugt et al., 2014). Whether this mechanism is applicable to long-range network interactions in the brain remains unproven, however.

Accordingly, **Study 5** of the present work, which will be detailed in section 3.5, will test if phase:amplitude coupling between alpha and gamma is a suitable neural mechanism for the orchestration of activity between different functional networks. The logic behind the model proposed and tested in **Study 5** is as follows: alpha phase from frontal medial regions like the anterior cingulate cortex (ACC) will define the periods for active engagement or disengagement of long-range functional networks. Importantly, ACC is considered part of the salience network, which function is to mediate the switching between fronto-parietal and default mode networks activity. Thus, if gamma activity from posterior regions pertaining either to the fronto-parietal or default mode networks is coupled to the excitatory part of alpha phase in ACC, active engagement will be achieved. Conversely, if posterior gamma activity is coupled to the inhibitory part of alpha phase active disengagement will be produced (Fig. 4). Therefore, in **Study 5** it is hypothesized that for young adults the excitatory part of frontal alpha phase should be coupled with fast oscillatory activity from posterior cortical regions of the fronto-parietal network during information maintenance in WM. This synchronization might allow for efficient information processing in the fronto-parietal network supporting WM, and, thus, promote an adequate execution of the experimental task. However, coupling between alpha and fast oscillatory activity might be altered in older adults causing decreased task performance. Therefore, it is expected that interregional cross-frequency coupling reflects the engagement of the DMN in the elderly.

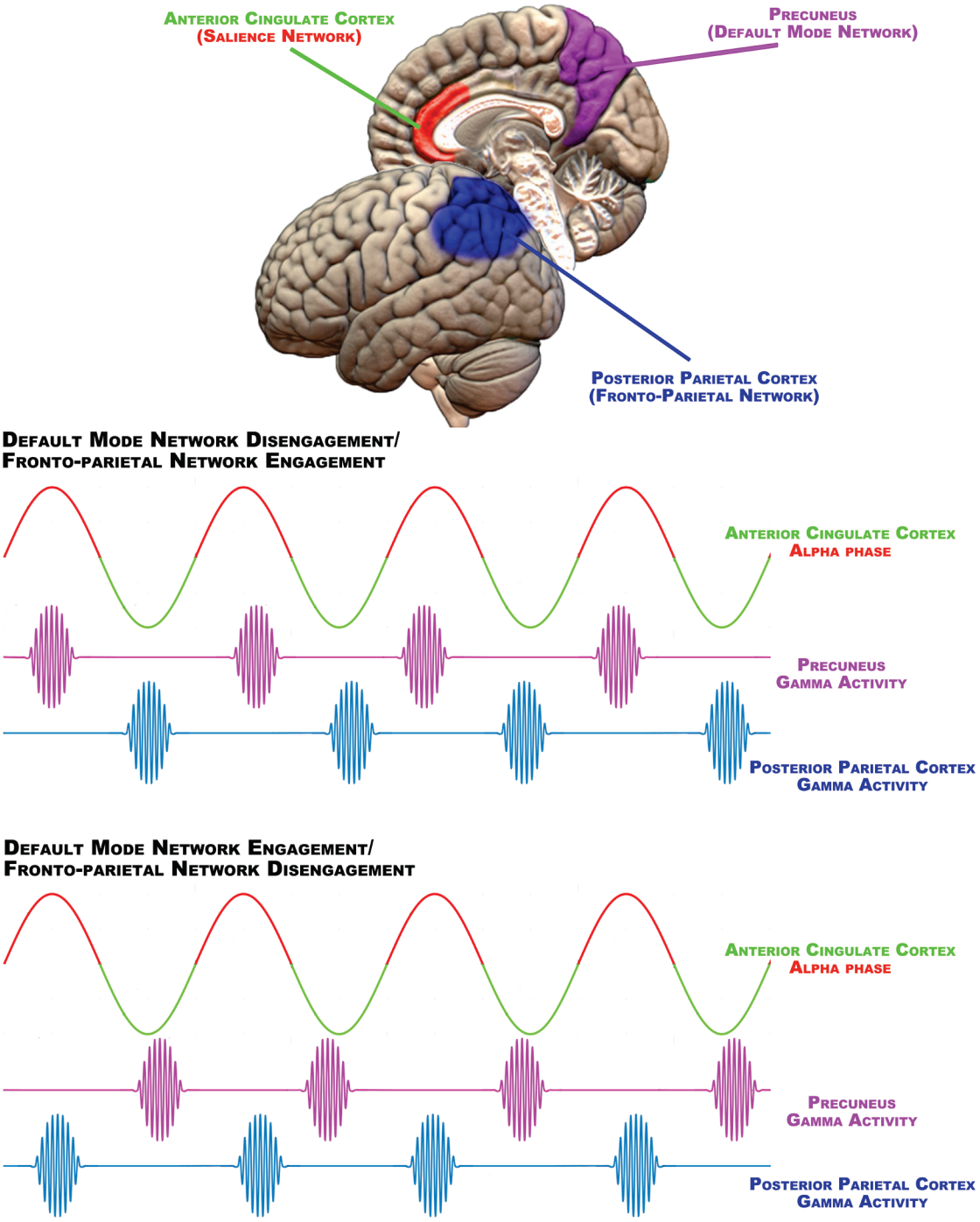


Figure 4. Schematic representation of the proposed neural mechanism for the top-down controlled orchestration of neuronal activity. Theoretically, in this model alpha phase from frontal regions (e.g. anterior cingulate) defines the periods for active engagement or disengagement of long-range functional networks due to the division of its cycles in an excitatory (green) and an inhibitory (red) part. Functional networks are engage when gamma activity from posterior brain regions pertaining either to the fronto-parietal network (e.g. posterior parietal cortex) or the default mode network (e.g. precuneus) is nested into the excitatory half of alpha phase from frontal sites, whereas disengagement is produced when posterior gamma activity is coupled with the inhibitory half of frontal alpha phase.

2. Research aims & Methods

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

The previous chapter highlighted the importance in this aging world of advance towards practices that help old adults maintain cognitive integrity as long as possible. For that purpose, it is basic to reach a detailed and thorough knowledge of cognitive processes, how they are carried out in the human brain and how they evolve along the lifespan. Indeed, given its role as foundation for high cognitive capacities and its high sensitivity to healthy aging related and pathological aging related downturns, visuospatial working memory is a priority target for research aiming to successfully overcome this challenge.

A promising way to address this objective is through electroencephalographic studies of brain activity in delayed match to sample tasks, since they enable researchers to capture the fast, dynamic and sequenced neural operations that constitute information encoding, maintenance and retrieval, independently of each other. Also they allow addressing questions related to the functional communication between different regions in the brain during the aforementioned cognitive events. Furthermore, it also enables researchers to easily manipulate and assess the effects of memory load and maintenance duration, two factors that sets the limits of working memory capacity. Nevertheless, despite there is a growing body of knowledge stemming from this research field there are still some unresolved issues that need further work to be clarified.

Consequently, in the present work a visuospatial delayed match to sample task adapted to electroencephalographic recordings was designed in order to assess several basic aspects of visuospatial working memory as well as to evaluate the impact of healthy normal aging on brain activity during encoding, maintenance and retrieval. The potential modulation of these effects by concurrent manipulations of memory load and maintenance duration was tested too. The specific aims that were expected to fulfill with this work are going to be presented in the next section.

2.1 RESEARCH AIMS

This work aims:

I- To study the event-related components related to information encoding and retrieval stages in visuospatial working memory, in order to determine a detailed time course of these processes (**Study 1**).

II- To investigate the possible modulatory effects that memory load and temporal duration of information maintenance in memory have on the ERP components identified for the brain electrical activity time course during encoding and retrieval (**Study 1**).

III- To examine brain electrical oscillatory activity during maintenance of visuospatial information in working memory and its modulations by working memory load. Particular interest is on alpha frequency band, since the relation and coexistence of different dynamics within this frequency band activity as well as their relation to working memory function are unclear (**Study 2**).

These first three objectives would serve to establish a firm base on which to study the effect of aging in brain electrical activity during the different cognitive events included in working memory.

IV- To analyze the effects of aging and their interaction with memory load and maintenance duration effects on task execution and on the parameters of the event-related potentials components associated with visuospatial information encoding and retrieval in working memory. This will help to delimitate the extent to which hypothesized age-related slowing of processing speed and working memory capacity reduction are applicable to these cognitive events (**Study 3** and **Study 4**).

V- To explore the differences among young and old adults in brain oscillatory activity during visuospatial information maintenance in working memory; as well as the potential relation of these differences with task execution changes. Specifically, analysis will focus on inter-regional phase:amplitude coupling of oscillatory activity, given its potential role in the orchestration of brain functional networks and in the maintenance of information in working memory (**Study 5**).

2.2 METHODS

Pursuing to reach these aims, a visuospatial DMS task was designed and used in all the experimental studies that are going to be presented in the next chapter. Two different samples of participants completed this task. That is, for **Study 1** and **Study 2**, which aimed to shed light on some basic aspects of WM function a sample of 29 young adults was recruited. In addition, for **Study 3**, **Study 4** and **Study 5**, which were devoted to the study of age-related changes in WM function, data from a sample of another 20 young and 20 older adults was collected. Therefore, as these aspects of the methodology are shared by all or, at least, part of the experimental studies, they are going to be presented in the following lines, prior to the chapter in which the studies are detailed.

2.2.1 Delayed match to sample task

As a task designed to assess the different cognitive events that build up WM function, the DMS task designed for this doctoral thesis comprised three stages: an encoding stage, a maintenance period and a retrieval/recognition stage. Figure 5 displayed an example of a trial in the DMS task. Each trial began with a 50 ms warning tone (1000 Hz). 500 ms later, the encoding stage includes the sample stimulus presentation on screen for 1000 ms. Following this, a stimulation-free period lasting 2500 or 5000 ms was used as maintenance period. Then, as retrieval/recognition stage, the probe stimulus was presented on screen until the participant executed the response or, if there was no response, for a maximum duration of 3000 ms. Finally, an inter-trial interval of 800 ms (between the participant's response and the warning tone) was interleaved between trials.

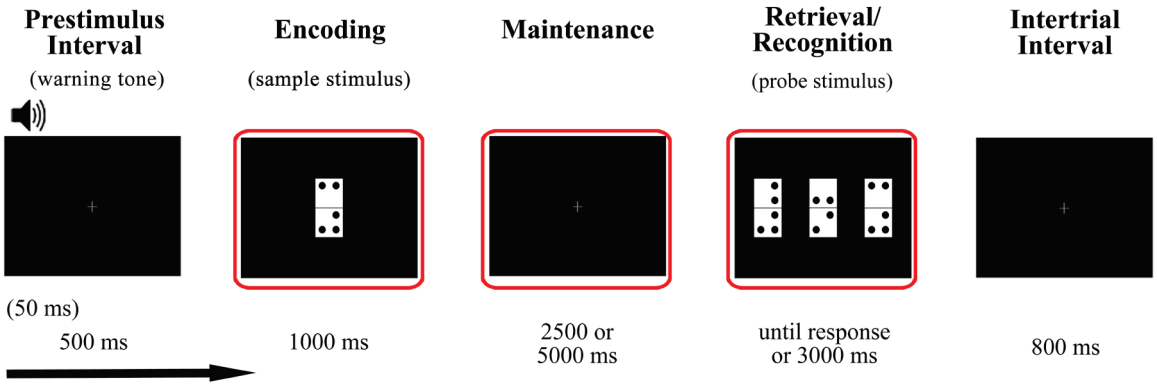


Figure 5. Schematic representation of a trial of the delayed match to sample task. Trials begin with a warning tone, followed 500 ms later by the presentation of a sample stimulus (a single domino tile) that has to be memorized. Then, a free stimulation period (maintenance) of 2500 or 5000 ms precedes the presentation of a probe stimulus (three dominoes), upon which participants have to retrieve information about sample stimulus to recognize the domino tile that is identical. The different stages analyzed in the experimental studies are enclosed in red squares.

In Figure 6, a detailed description of the stimuli employed in the DMS task can be found. All stimuli were adapted domino tiles. These tiles displayed a varied number of dots in different spatial configurations; consequently the adapted domino tiles taxed visuospatial abilities and enable a simple manipulation of their memory load content. Further, these adapted domino tiles were used for two different stimulus presentations during a single task trial; namely, the sample stimulus and the probe stimulus. It is noteworthy that a fixation cross was presented in the center of the screen whenever there was no stimulation in an attempt to reduce ocular artifacts.

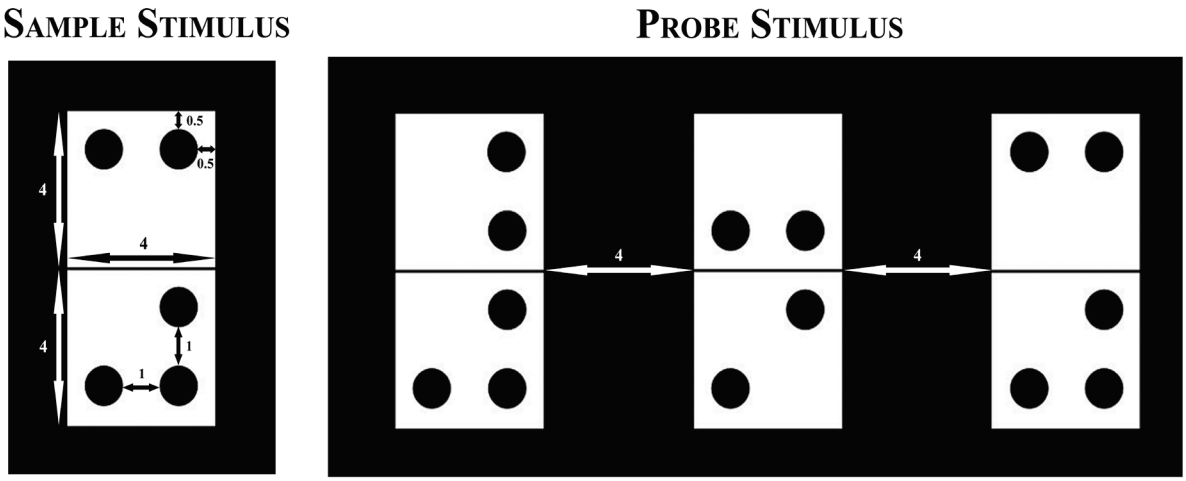


Figure 6. Characteristics and dimensions of sample and probe stimulus. Example of a sample (left) and probe (right) stimulus, in this case of the high memory load condition. Numbers next to the arrows indicate distances in centimeters.

On the one hand, sample stimulus consisted on the presentation of a single adapted domino tile on a black background. This tile was rectangular, composed by two equally sized white squares arranged vertically. The total dimensions were 8 cm long and 4 cm

wide and, accordingly, each square was 4 cm long and 4 cm wide. The interior of each white square contained between 0 and 3 dots, which were positioned in one out of four different possible locations, one per corner of the square. These dots were black and were located 0.5 cm from the edges of the tile and 1 cm from each other.

On the other hand, probe stimulus presentation comprised three tiles of the same structure as those used in the sample stimulus (i.e. with the same dimensions). The three tiles were at a distance of 4 cm from each other and placed in the center and on the right and left of the black background. Only one of the tiles was designed as the target, and, thus, was identical to that presented as sample stimulus in the same trial. The position of the target in probe stimulus presentation was counterbalanced, so that it did not appear in the same position in more than three consecutive trials.

All the task trials were presented on a 19" computer monitor (100 Hz refresh rate) placed at a 1 m distance from the eyes of the participant, who was sat in a comfortable armchair inside a Faraday chamber with attenuated levels of light and noise. Participants were asked to memorize (encode) the configuration of dots inside the tile presented as sample stimulus. Then, they must actively maintain this information in mind during the stimulation free (maintenance) period. Finally, participants were asked to retrieve this information in order to identify the target among the three domino tiles that formed the probe stimulus. Once the target was identified participants were instructed to press, as quickly and accurately as possible, the button corresponding to the position of the target in the screen (left, center or right) using a respond pad (Cedrus®, model RB-530) with three horizontally arranged buttons. Further, participants were also instructed to use their left hand to press the left button and the right hand to press the other two buttons (right was the dominant hand in all but 6 out of 60 participants). In order to confirm that they had understood the instructions and to familiarize them with the experimental environment, participants completed a short training in the task prior to the EEG recording. The presentation of stimuli and response recording were controlled by Presentation® software (Neurobehavioral Systems, Inc., Albany, CA, USA).

The DMS task comprised 200 trials divided into two blocks, which takes no longer than 30 minutes, including a 5 minutes break between blocks, to complete the task. The two task blocks differed in the memory load of their stimuli. The first block was always the low memory load block, which included 90 trials in which dominoes with 2 or 3 dots in total (76 possible combinations) were used. The second block was always the high memory load block, and consisted of 110 trials with dominoes that included 4 or 5 dots in total (116 possible combinations). Remarkably, in the high memory load block, the use of domino tiles with two dots in each half was limited. That is, to avoid simple and easily verbalized configurations, only dominoes with the dots in one of the halves forming a diagonal were used (100 possible combinations). As the number of possible combinations was lower than the number of trials in each block, 20% of the trials in each block included as sample

stimulus a domino that was also present as sample stimulus in another trial. In addition, as it was expected that participants would make more errors in the high memory load block than in the low memory load block, more trials were included in the former to ensure a good signal to noise ratio for ERPs calculation.

Finally, half of the trials in each block have a maintenance period of 2500 ms, and were grouped in the short maintenance period condition. The other half of trials in each block formed the long maintenance period condition, which comprised trials with a maintenance period of 5000 ms. The probability of appearance of both duration times was the same (50%) and both were distributed pseudo-randomly, to avoid more than five consecutive trials having the same maintenance period duration.

2.2.2 Sample characteristics

Two samples were recruited for participation in the experimental studies that are presented in this doctoral thesis. All these participants gave their informed consent to participating in the study, and the study protocol was approved by the ethical Committee at the University of Santiago de Compostela (USC). None of the participants were taking psychotropic medication or reported history of neurological or psychiatric disorders. Also, they all have normal or corrected to normal vision. Additionally, they were instructed to abstain for alcohol and caffeine the day before the experimental session. Before performing the DMS task while recording the EEG, participants filled some demographic data in a form and were evaluated with the Edinburgh Handedness Inventory (Oldfield, 1971) and the Spanish version of the Wechsler Adults Intelligence Scale vocabulary subtest ([WAIS], Wechsler, 1997). Table 1 reports these data.

Table 1. ***Demographic and evaluation data for the two samples.***

		N	Male/ Female	Right handed	Age	Vocabulary score	Years of formal education
SAMPLE 1	Young Adults	29	9/20	26	20.5±2.8	51.1±4.9	14.7±1.6
SAMPLE 2	Old Adults	20	4/16	20	67.8±7.7	48.1±8.7	14.1±3.9
	Young Adults	20	4/16	17	23.8±3.2	47.9±5.2	16.2±1.2

N: number of participants. Male/Female: raw numbers for each gender. Handedness is based on the Edinburg Handedness Inventory (Oldfield, 1971). Age: mean ± standard deviation. Vocabulary score: corresponding to the Spanish version of the WAIS vocabulary subtest. Mean ± standard deviation. Years of formal education: mean ± standard deviation.

The sample of 29 young adults that was used for **Study 1** and **Study 2** was recruited from students at the USC. Similarly, the 20 young adults group of the sample employed for **Study 3**, **Study 4** and **Study 5** was recruited from USC alumni. The 20 older adults of this

latter sample were recruited from the USC courses for older adults and from two different cultural associations in which they regularly participate in cognitively demanding activities (e.g. learning a foreigner language, informatics course, etc.). The two age groups of the second sample (i.e. the 20 young and the 20 old adults) significantly differed in time spent in formal education [$t(18.79) = -2.160$, $p \leq .044$], but were equated in their scores of the Spanish version of the WAIS vocabulary subtest [$t(31.41) = 0.89$, $p \leq .930$].

It is noteworthy here that there were some aspects of EEG recordings that were common to both samples. For instance, all electrodes were placed in the standard positions of the international 10-10 system. Electrode montage included fronto-polar ground and nose tip reference and all the electrode impedances were maintained below 10 kΩ. Further, in all the recordings, EOG activity was monitored with two electrodes placed at the outer canthi of both eyes (HEOG) and another two electrodes placed above and below the right eye (VEOG). Also, the EEG signal was analogically filtered between 0.01 to 100 Hz and sampled at 500 Hz for all recordings. However, EEG data from the two samples were recorded with different electrodes and caps. EEG from the first sample (i.e. 29 young adults) was recorded using 49 active electrodes inserted in an Easycap (GmbH), whereas EEG signals from the second sample (i.e. 20 young and 20 older adults) were recorded through 51 active electrodes inserted in an Acticap (GmbH). Consequently, comparison between samples would not be advisable given the differences in the montage and in the technical specifications of the electrodes and caps.

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

3. Experimental studies

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

3.1 STUDY 1

Pinal, D., Zurrón, M. & Díaz, F. (2014). Effects of load and maintenance duration on the time course of information encoding and retrieval in working memory: from perceptual analysis to post-categorization processes. *Frontiers in Human Neuroscience, 8* (Article 165). doi:10.3389/fnhum.2014.00165.

Como se destacou na introdución, unha das debilidades dos modelos neurobiolóxicos da memoria de traballo (MT) viso-espacial é a falta dunha fonda comprensión da dinámica temporal dos procesos de codificación, mantemento e recuperación da información. Ademais, os estudos que combinaron tarefas de emparellamento demorado (ED) coa técnica dos potenciais evocados (PE) para investigar a modulación da actividade eléctrica cerebral pola carga en memoria e a duración do período de mantemento nestes tres procesos, ou son escasos ou teñen arroxado resultados contrapostos. Así é que o debate ó redor destes aspectos básicos da MT viso-espacial segue aberto, polo que neste traballo de doutoramento pretendeuse arroxar algo de luz ó respecto. Concretamente, como xa ven de sinalarse, o obxectivo I pretende examinar a estrutura temporal da codificación e a recuperación de información, mediante a análise de compoñentes principais (ACP) dos PE recollidos nestes eventos cognitivos. E o obxectivo II, pretende estudar como os compoñentes revelados pola anterior análise son modulados pola carga en memoria e a duración do período de mantemento.

Deste xeito, este primeiro estudo experimental recolle as análises realizadas para dar resposta a eses dous primeiros obxectivos. A tal fin, presentouse unha tarefa ED viso-espacial a unha mostra de 29 mozos sans, durante a cal rexistrábase a sinal electroencefalográfica (EEG) e a execución (i.e. taxa de acertos e tempos de reacción). Para o estudo dos efectos da carga en memoria e da duración do período de mantemento da información, empregáronse as dúas condicións de carga en memoria (alta e baixa) e as dúas de duración do período de mantemento da información (longa e curta) descritas no capítulo de obxectivos e método.

A fin de determinar dunha forma obxectiva os compoñentes do curso temporal dos PE durante a codificación e a recuperación, os datos do EEG analizáronse mediante unha ACP temporais. Amais, para a análise dos efectos da carga en memoria e da duración do período de mantemento sobre a execución, a porcentaxe de acertos e os tempos de reacción foron combinados nunha única medida: as puntuacións de eficiencia inversa (EI). Esta puntuación é igual ó tempo de reacción medio partido pola proporción de acertos, e empregase para evitar efectos debidos a cambios no criterio de resposta ou no compromiso entre velocidade e precisión da resposta. Ditas puntuacións foron, pois, comparadas entre condicións de carga en memoria e entre condicións de duración do período de mantemento. Do mesmo xeito, os efectos destas variables sobre os compoñentes dos PE avaliáronse coa comparación entre condicións de carga e entre condicións de duración do período de

mantemento da latencia a pico e das puntuacións de factor dos compoñentes identificados pola ACP temporais. As puntuacións de factor, empréganse como equivalentes ós valores de amplitude dos compoñentes dos PE, e son un dos parámetros resultantes da ACP. Esta análise complementouse co uso de tomografía electromagnética de baixa resolución (LORETA), que permitiu comparar a activación estimada para as fontes xeradoras da actividade EEG rexistrada no coiro cabeludo entre as dúas condicións de carga e as dúas de duración do período de mantemento.

Os resultados da ACP permitiron determinar de forma obxectiva o curso temporal da actividade cerebral durante a codificación e recuperación de información viso-espacial en MT. Estes resultados amosaron que a actividade cerebral é similar durante a codificación e a recuperación. En ámbolos casos a estrutura temporal componse de seis factores temporais, que coinciden en latencia e distribución no coiro cabeludo cos compoñentes dos PE: P1, N1, P2, N2, P300 e unha onda lenta positiva durante a codificación e negativa durante a recuperación.

Polo que se refire ós efectos da carga en memoria na execución da tarefa, esta foi peor (maior puntuación EI) na condición de alta que na de baixa carga en memoria. Así é que, en liña con estudos previos, unha maior carga en memoria acompañouse dunha execución menos eficiente na tarefa ED.

Tamén, os parámetros dalgúns compoñentes dos PE foron modulados por este factor. Así, a amplitude de P300 foi menor na condición de alta que na de baixa carga en memoria durante a codificación e a recuperación. En troques, a amplitude da onda lenta foi maior na condición de alta que na de baixa carga en memoria durante a codificación, en tanto que a de N2 foino durante a recuperación. Deste xeito, parece que, a carga en memoria non afecta os compoñentes dos PE relacionados co procesamento perceptivo (i.e. P1 e N1) durante a codificación nin durante a recuperación. Non obstante, si parece modular a distribución de recursos de procesamento entre compoñentes máis tardíos e relacionados coa avaliación e categorización dos estímulos, así como con procesos de elaboración ou refresco do material en memoria. Así, durante a codificación de información viso-espacial en MT, unha alta carga en memoria reduce os recursos de procesamento para a categorización do estímulo ó seren captados por procesos de elaboración e mantemento da información, o cal reflíctense na reducida amplitude de P300 e o incremento na amplitude da onda lenta positiva, respectivamente. Durante a recuperación de información viso-espacial, recrutáronse máis recursos para a clasificación do estímulo en condicións de alta que de baixa carga, reducíndose a cantidade de recursos dispoñibles para a categorización do estímulo; segundo reflicten a maior amplitude de N2 e a menor de P300.

A carga en memoria produciu, así mesmo, variacións na activación cerebral, en concreto do lóbulo frontal durante a codificación e a recuperación de información. Os resultados parecen indicar que a carga en memoria acompañouse en diferentes momentos da codificación e recuperación de información dunha redución da actividade en rexións

frontais asociadas a aspectos do procesamento da información que son irrelevantes para a tarefa (e.g. frontal medial e partes do córtex cingulado anterior). En tanto que, durante a recuperación e coincidindo coa latencia de N2, unha maior carga en memoria acompañouse dun aumento da actividade en áreas que teñen sido relacionadas con procesos de coordinación da atención prestada a representacións mentais e a estímulos externos (i.e. xiro frontal medio correspondente á área 10 de Brodmann).

Por último, en relación cos efectos da duración do período de mantemento, os resultados amosaron que esta non tiña efectos sobre a execución condutual na tarefa ED. Así é todo, períodos de mantemento máis longos asociáronse a un incremento nos recursos para a discriminación e clasificación do estímulo, a xulgar pola maior amplitude de N2 e a maior actividade no córtex temporal superior esquerdo nesta condición que na de duración curta. Ademais, a latencia de P300 foi menor nesta última condición que na de duración longa do período de mantemento. Deste xeito, parece que os resultados da análise dos efectos da duración do período de mantemento son complexos, e requirirase de futuros traballos para valorar as predicións feitas dende as teorías do decaemento baseado no tempo, as cales suxiren unha debilitación dos trazos de memoria co paso do tempo, producindo un deterioro da execución e cambios perniciosos na actividade eléctrica cerebral tras períodos longos de mantemento.

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

This study has been published in Frontiers in Human Neuroscience. Its complete reference is:

Pinal, D., Zurrón, M. & Díaz, F. (2014). Effects of load and maintenance duration on the time course of information encoding and retrieval in working memory: from perceptual analysis to post-categorization processes. *Frontiers in Human Neuroscience, 8* (Article 165). doi:10.3389/fnhum.2014.00165.

Further, this work can be accessed (open access) via the following link:

http://journal.frontiersin.org/article/10.3389/fnhum.2014.00165/full

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

3.2 STUDY 2

Crespo-García, M., **Pinal, D**., Cantero, J. L., Díaz, F., Zurrón, M. & Atienza, M. (2013). Working Memory Processes Are Mediated by Local and Long-range Synchronization of Alpha Oscillations. J*ournal of Cognitive Neuroscience, 25*(8), 1343-1357. doi:10.1162/jocn_a_00379.

O primeiro estudo deste traballo de doutoramento pretendeu dar resposta os obxectivos I e II, para o que analizou a actividade eléctrica cerebral durante a codificación e a recuperación de información viso-espacial en memoria de traballo. Así é que, para rematar a análise dos aspectos básicos da MT viso-espacial resaltados durante o capítulo introdutorio, neste segundo estudo procurouse dar resposta ó obxectivo III. Deste xeito, o presente estudo ten como propósito examinar a actividade eléctrica cerebral durante o mantemento de información en memoria, e avaliar as modulacións que se producen nesta en relación con cambios na carga en memoria. Máis concretamente, debido á diversidade de respostas observadas na banda de frecuencia alfa en resposta a aumentos na carga en memoria (i.e. reducións da potencia en rexións posteriores, así como aumentos da potencia en rexións posteriores e frontais), este estudo pretende determinar se estas diferentes manifestacións dependentes da carga en memoria nas dinámicas da amplitude da banda alfa poden reflectir diferentes aspectos de procesos inhibitorios que coexisten en diferentes rexións corticais durante o mantemento de información.

Con tal propósito, fixose uso dos mesmos datos electroencefalógraficos e condutuais que no **Estudo 1**. Isto é, os datos correspondentes á mostra de 29 mozos sans que completaron a tarefa de ED, na que a manipulación do número e configuración espacial dos puntos contidos nunha ficha de dominó permitiunos crear dúas condicións de carga en memoria. Neste **Estudo 2**, os datos de execución; é dicir, proporción de acertos e tempos de reacción, relacionáronse cos datos da actividade cerebral. O sinal EEG, pola súa banda, foi analizado no dominio tempo-frecuencia. Para iso, empregouse a análise de mínimos cadrados parciais, que permitiu determinar de forma obxectiva os diferentes factores da actividade oscilatoria asociados ó mantemento de información en memoria (i.e. ó contrastar a actividade de liña base coa rexistrada durante o período de mantemento) así como os asociados ás manipulacións na carga en memoria (i.e. ó contrastar a actividade nas dúas condicións de carga en memoria). Amais, a utilización dun filtro espacial (beamformer) aplicado ó sinal rexistrado no coiro cabeludo, permitiu avaliar as dinámicas da actividade alfa durante o mantemento de información ó nivel das súas fontes xeradoras. Finalmente, o cálculo do índice de diferenza de fase permitiu determinar a relación que existía na fase de alfa entre diferentes rexións corticais. Deste modo, analizouse a existencia de sincronía entre diferentes rexións corticais, así como as diferenzas nesa sincronía producidas pola carga en memoria.

Os resultados do contraste da actividade durante un período de liña base (i.e. no intervalo entre ensaios) e a actividade cerebral do período de mantemento revelaron incrementos independentes da carga en memoria na potencia de alfa durante o mantemento, así como na sincronía interrexional da súa fase entre áreas irrelevantes para a tarefa situadas en rexións corticais posteriores próximas ó suco parieto-occipital (cuneus e precuneus/cingulado posterior). Así pois, estas variacións na actividade de alfa correspóndense cos diferentes factores que compoñen, de forma obxectiva, a actividade oscilatoria asociada ó mantemento de información viso-espacial en MT. Amais, estas modulacións en rexións irrelevantes para a tarefa e independentes da manipulación da carga en memoria, apoian o papel das oscilacións alfa na inhibición do procesamento sensorio-motor irrelevante para a tarefa cando un participante está activamente involucrado na realización dunha tarefa.

Os resultados do contraste entre condicións de carga en memoria amosaron diminucións dependentes da carga en memoria na potencia de alfa en áreas do córtex prefrontal esquerdo e da cortiza parietal posterior de xeito bilateral. Estas diminucións, amais, eran precedidas no tempo por reducións dependentes da carga na sincronía da fase de alfa entre o córtex prefrontal esquerdo e a cortiza parietal posterior esquerda. Na análise da sincronía entre estas dúas rexións observouse unha diferenza de 15 ms na latencia da fase de alfa, a cal indica que o ciclo de alfa no córtex prefrontal esquerdo antecede ó da cortiza parietal posterior. Xa que logo, a carga en memoria parece modular a actividade oscilatoria durante o mantemento de información viso-espacial en MT. Estas variacións dependentes da manipulación da carga en memoria indican que a actividade alfa pode ser un índice de procesos de inhibición que facilitan o mantemento dos estímulos a través da redución da inhibición en áreas relevantes para a tarefa, e a través de sinais "arriba-abaixo" para o control de ditos procesos inhibitorios. Deste xeito, estes resultados probablemente reflictan un mecanismo no que, debido o aumento das demandas ó incrementarse a carga en memoria, áreas parietais relevantes para a o procesamento de información requirido pola tarefa son liberadas da inhibición exercida por mecanismos de control "arriba-abaixo" (i.e. mecanismos de control exercidos polo córtex prefrontal).

Finalmente, cabe salientar, que non se atoparon relacións entre a actividade cerebral e a execución condutual.

Así é que, de forma conxunta, os achádegos do presente traballo parecen indicar que é posible a coexistencia de diferentes dinámicas na actividade de alfa en diferentes rexións corticais durante o período de mantemento de información nunha mesma tarefa. Deste xeito, estes resultados suxiren que a actividade alfa reflicte un compoñente esencial do mantemento de información viso-espacial en MT, o cal probablemente actúe inhibindo o procesamento en áreas posteriores irrelevantes para a tarefa. Este compoñente, amais, complementase cunha diminución da inhibición do procesamento nas areas relevantes para a tarefa que se produce a través de mecanismos "arriba-abaixo" e de xeito dependente da

demanda cognitiva. Polo tanto, as diferentes dinámicas da amplitude e da fase de alfa en redes corticais locais e de longa distancia reflicten diferentes mecanismos neurais do control "arriba-abaixo", os cales poden ser cruciais na mediación dos diferentes procesos de memoria de traballo, e, en particular, do mantemento da información viso-espacial.

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

This study has been published in the Journal of Cognitive Neuroscience. Its complete reference is:

Crespo-García, M., **Pinal, D**., Cantero, J. L., Díaz, F., Zurrón, M. & Atienza, M. (2013). Working Memory Processes Are Mediated by Local and Long-range Synchronization of Alpha Oscillations. J*ournal of Cognitive Neuroscience, 25*(8), 1343-1357. doi:10.1162/jocn_a_00379.

Further, this work can be accessed (under subscription) via the following link:

http://www.mitpressjournals.org/doi/full/10.1162/jocn_a_00379

UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

3.3 STUDY 3

Pinal, D., Zurrón, M. & Díaz, F. (under review in Frontiers in Aging Neuroscience). Age-related changes in brain activity are specific for high order cognitive processes during successful encoding of information in working memory.

Este terceiro estudo do presente traballo de doutoramento, é o primeiro que tratará sobre os efectos do avellentamento san sobre a MT viso-espacial e a actividade cerebral que a soporta. Así pois, este **Estudo 3** e o posterior **Estudo 4** foron deseñados para dar resposta o obxectivo IV, o cal céntrase nos efectos da idade e na súa interacción cos efectos da carga en memoria e da duración do período de mantemento na actividade eléctrica cerebral durante a codificación e a recuperación de información viso-espacial en memoria de traballo. De esta forma, e dada a escaseza de estudos que analizaron cada un destes dous eventos cognitivos por separado, no presente **Estudo 3** realizouse unha avaliación dos efectos da idade na actividade eléctrica cerebral durante a codificación, onde se supón concéntranse a maior parte de ditos efectos.

Máis concretamente, este estudo pretende avaliar, por unha banda, se a través da manipulación experimental da carga en memoria atópanse evidencias electrofisiolóxicas dunha menor capacidade da MT en adultos maiores que en mozos, posto que este aspecto é central nalgunhas hipóteses explicativas do declive asociado a idade nas capacidades cognitivas e non foi analizando con anterioridade. E por outra banda, pretende examinar se, en liña cos resultados de estudos previos, existe unha diminución xeneralizada da velocidade do procesamento neural durante a codificación de información e na resposta á tarefa.

Para lograr estes obxectivos, rexistrouse a actividade EEG e os datos de execución (i.e tempos de reacción e proporción de acertos) dunha mostra de 20 mozos e 20 adultos maiores sans namentres executaban a tarefa de emparellamento demorado empregada e validada nos dous estudos previos. Os datos de execución foron comparados entre grupos e entre condicións de carga. En canto á actividade cerebral, recolléronse as latencias a pico e amplitudes de liña base a pico dos compoñentes dos PE que foron identificados no **Estudo 1** como parte do curso temporal da actividade eléctrica cerebral durante a codificación (i.e. P1, N1, P2, N2, P300 e unha onda lenta positiva). Ditos parámetros tamén foron comparados entre grupos e condicións de carga en memoria. Por último, os parámetros que mostraron diferenzas significativas entre grupos correlacionáronse cos tempos de reacción e coas proporcións de acertos.

As probas estatísticas realizadas no presente estudo amosaron que as taxas de precisión na resposta á tarefa foron máis baixas e os tempos de reacción máis longos para os adultos maiores que para os mozos. Á beira disto, a precisión na resposta á tarefa foi menor na condición de alta que na de baixa carga en memoria de traballo, pero só nos adultos maiores. Así pois, os resultados condutuais apoian a existencia dun declive da MT

viso-espacial coa idade, así como dunha diminución na velocidade coa que os adultos maiores completaron a tarefa. E mais aínda, estes resultados suxiren que os adultos maiores son máis sensibles ás manipulacións da carga en memoria que os mozos.

Porén, a interacción entre a carga en memoria e a idade non tivo efectos significativos sobre a actividade cerebral. Tampouco houbo diferenzas entre ambos grupos de idade para as amplitudes e latencias dos compoñentes P1 e N1. Non obstante, as latencias de P2 e N2 foron máis longas nos participantes maiores que nos mozos. Os resultados tamén revelaron que os adultos maiores presentaban menores amplitudes que os mozos nos compoñentes P2 e P300.

Desta forma, os resultados observados para os compoñentes dos PE durante a codificación de información viso-espacial en MT parecen indicar que o procesamento perceptivo, reflectido nas latencias e amplitudes de P1 e N1, está preservado no cerebro humano avellentado. De forma similar, a ausencia de interaccións da idade e da carga en memoria, parecen suxerir que durante a codificación de información o procesamento neural da información nos maiores non é máis sensible á carga en memoria que o dos mozos. Agora ben, parece haber unha diminución da velocidade de procesamento asociada á idade que afecta de maneira específica ós procesos de análise e avaliación do estímulo, a tenor das maiores latencias de P2 e N2 (respectivamente) que se observaron nos maiores. Así mesmo, as menores amplitudes de P2 e P300 nos maiores, parecen indicar a existencia dunha diminución asociada á idade na mobilización ou na cantidade de recursos de procesamento dispoñibles para a avaliación e categorización dos estímulos.

Alén disto, en canto á relación dos correlatos da actividade neural cos datos de execución na tarefa, observouse que a latencia de N2 relacionábase directamente coa precisión nas respostas á tarefa cando se controlaron os efectos da idade cronolóxica. Isto é, a maior latencia de N2, maiores taxas de acerto. Amais, cálculos realizados por separado para cada grupo de idade revelaron que esta relación só era significativa nos adultos maiores. Deste xeito, cando a latencia de N2 era máis longa, observouse unha maior precisión na execución da tarefa de emparellamento demorado, especialmente nos adultos maiores. Así pois, os resultados do presente estudo demostraron que a actividade durante a codificación de información viso-espacial en MT relacionase ca execución na tarefa. En concreto, o tempo empregado na avaliación do estímulo relacionouse coa precisión na resposta, sobre todo nos adultos maiores.

En conxunto, os resultados do presente estudo apoian a existencia dunha diminución da velocidade do procesamento asociada á idade, se ben esta limitouse ós procesos de análise e avaliación do estímulo, e por tanto non pode dicirse que fora xeneralizada. Amais, a duración deses procesos de avaliación do estímulo asociouse coa execución da tarefa, especialmente no grupo de maiores, que pareceron necesitar máis tempo que os mozos para completar de forma eficiente e satisfactoria a avaliación dos estímulos. Amais, os resultados tamén parecen indicar que existe unha diminución asociada á idade na

cantidade de recursos de procesamento dispoñibles ou na súa mobilización cara procesos de avaliación e categorización dos estímulos. Pola contra, inda que na execución condutual os adultos maiores parecen máis sensibles á carga en memoria, os compoñentes dos PE durante a codificación de información viso-espacial non mostraron dita sensibilidade ás manipulacións da carga en memoria.

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

Age-related changes in brain activity are specific for high order cognitive processes during successful encoding of information in working memory

Diego Pinal[1*], Montserrat Zurrón[1] and Fernando Díaz[1]

1 Laboratory of Cognitive Neuroscience, Department of Clinical Psychology and Psychobiology, Universidade de Santiago de Compostela, Santiago de Compostela, Galiza, Spain.

***Correspondence**:
Mr. Diego Pinal
Department of Clinical Psychology and Psychobiology,
Facultade de Psicoloxía, Universidade de Santiago de Compostela
Rúa Xosé María Suárez Núñez, s/n. Campus Sur.
Santiago de Compostela, 15782. Spain
diego.pinal@usc.es

RUNNING TITLE

Age-related differences in WM encoding

ABSTRACT

Memory capacity suffers an age-related decline. Information encoding in memory has been demonstrated to be very sensitive to age-related changes, especially when carried out through self-initiated strategies or under high cognitive demands. However, most ERP research on age-related changes in working memory (WM) has used tasks that preclude distinction between age-related changes in encoding and retrieval processes. Here, we used ERP recording and a delayed match to sample (DMS) task with two levels of memory load to assess age-related changes in electrical brain activity in young and old adults during successful information encoding in WM. The accuracy of task performance was lower for high than for low memory load conditions only in the old adults. However, the interaction between WM load and age did not have any significant effect on brain activity. In addition, accuracy rates were lower and reaction times were longer for old than for young adults. Regarding brain activity, there were no differences between age groups for P1 or N1 amplitude and latency, indicating that perceptual processing is preserved in the aging human brain. However, P2 and N2 latencies were longer in old than in young participants, demonstrating a specific slowing of processing speed in target stimulus analysis and evaluation processes. The results also revealed smaller P2 and P300 amplitudes that may signal an age dependent reduction in the processing resources available for stimulus evaluation and categorization. Moreover, N2 latency was directly related to response accuracy when chronological age was controlled for, although separate calculations for each age group showed that this relation was only significant in the old adults. Consequently, longer N2 latencies, which are associated with stimulus analysis and evaluation processes, were related to greater accuracy of performance of the DMS task, especially in old adults.

KEYWORDS

Event-related potentials, working memory, encoding, aging, executive functions, slowing of processing.

I) INTRODUCTION

As we age some of our mnemonic abilities suffer a decline (for review, see Park et al., 2002; Glisky, 2007; Fabiani, 2012). Such abilities include working memory (WM), which has been defined as the ability to hold in mind and/or manipulate for brief periods of time small amounts of information that are no longer available in our environment (Baddeley & Hitch, 1974; Baddeley, 2012). Moreover, WM is thought to comprise three different cognitive events: information encoding, information maintenance and information retrieval (for a review see Jonides et al., 2008).

The decline in WM due to normal aging processes is indicated by lower accuracy rates and longer reaction times in performance of experimental tasks used to assess this ability (Baltes et al., 1999; Park et al., 2002). Several explanatory hypotheses have been proposed to account for this decline. For instance, it has been suggested that it may be caused by a general slowing of processing speed in old adults (Rousselet et al., 2009; Salthouse, 1996), and/or by deficits in frontal lobe function, which, in turn, give rise to alterations in executive control, e.g., deficits in the selection of relevant information or in the capacity to actively maintain goal relevant information (Hasher & Zacks, 1988; Kalkstein, Checksfield, Bollinger, & Gazzaley, 2011; Paxton et al., 2008; West, 1996).

Several authors have suggested that such age-related decline in WM is mainly caused by changes in brain activity during information encoding into memory (Craik & Rose, 2012; Finnigan et al., 2011; Friedman et al., 2007), especially when the encoding strategies are self-initiated, i.e., when there are no specific instructions about how to encode information (Craik & Rose, 2012; Friedman et al., 2007; Hashtroudi et al., 1989). Moreover, differences in mnemonic capacities associated with normal aging are enhanced in tasks that impose high demands in cognitive abilities, such as those in which memory load is manipulated, i.e., when large amounts of information must be held in memory or when such information is complex (Buckner, 2004; Gazzaley, Sheridan, Cooney, & D'Esposito, 2007; Oberauer & Kliegl, 2001). Indeed, some authors have suggested that old adults are more sensitive to cognitive demands than young adults, and they therefore show signs of cognitive effort at lower levels of demand than young adults (Cabeza & Dennis, 2013; Park & Reuter-Lorenz, 2009).

The use of event-related potentials (ERP) enables analysis of electrical brain activity with a temporal resolution and precision in the order of a few milliseconds. Consequently, this technique is a potentially useful tool for studying the different neural processes underlying information encoding in WM.

Most ERP research on normal aging related changes in brain activity has used the oddball paradigm, which evaluates attentional and stimulus discrimination processes. Of those focusing on age-related changes in WM, n-back tasks appear to be the most common experimental paradigm. Unfortunately, n-back tasks preclude distinction between

information encoding and information retrieval. Nevertheless, this can be overcome by using other tasks such as Sternberg's tasks (Sternberg, 1966) and delayed match to sample tasks (DMS) (John et al., 1996), both of which include a stage when information must be encoded and actively held in mind and a separate later stage when information must be retrieved in order to complete some kind of judgment (e.g., same vs different, present vs absent, …).

Using the Sternberg paradigm, Finnigan et al. (2011) found that for words that have to be encoded in WM, the P1 latency was longer and N1 amplitude was larger in old adults than in young adults. However, during the information encoding stage in a DMS task, Gazzaley et al. (2008) and Zanto et al. (2010) did not observe any age-related differences in P1 component latency or amplitude, although they observed longer N1 latencies. Also in contrast to the findings of Finnigan and coworkers, Zanto et al. (2010) reported lower N1 amplitude in old than young adults. Longer P1 (Finnigan et al., 2011) or N1 (Gazzaley et al., 2008; Zanto et al., 2010) latencies for old than for young participants have been interpreted as evidence for a generalized slowing of processing speed in old adults. However, the age-related effects on these ERP components during information encoding in WM are still unclear, as the results of these studies are at least partly contradictory.

Furthermore, in young adults, P1 and N1 components have been shown to be sensitive to memory load changes during information encoding in WM (Morgan et al., 2008). Nevertheless, to our knowledge, no studies have assessed the possible interactions between memory load and the age-related effects on these ERP components

Regarding later ERP components, which have been related to high order cognitive processes, several studies using n-back tasks have demonstrated that fronto-central P2 and N2 components are sensitive to aging effects on WM processes (McEvoy et al., 2001; Missonnier et al., 2004, 2011). However, there is some controversy about how normal aging modulates these components. Therefore, although McEvoy et al. (2001) observed higher P2 amplitude in old adults, Missonnier et al. (2004, 2011) found that the area delimited jointly by P2 and N2 components was lower in old than in young adults. Furthermore, in McEvoy and coworkers study (McEvoy et al., 2001), memory load (defined as the number of previous trials in which target was defined) had no effects on P2 amplitude, whereas the area under P2-N2 complex increased with memory load in young but not in old adults in Missonnier and coworkers experiments (Missonnier et al., 2004, 2011). Hence, the effect of any interaction between memory load and aging on these components amplitude is also unclear.

Concerning the P300 component, in studies involving n-back tasks, McEvoy et al. (2001) and Saliasi et al., (2013) observed longer latencies and lower amplitudes, at parietal electrodes, for old than young adults. In a DMS task, Gazzaley et al. (2008) observed longer P300 latency in old than young participants. These results are consistent with the effects of age on P300 ERP component that has been repeatedly validated regardless of the

task used (for reviews, see Polich, 1996; Friedman, 2012). Such age-related effects on P300 have been considered to indicate a reduction in the availability of processing resources and of a slowing in stimulus evaluation and categorization timing (Lorenzo-López, Amenedo, Pascual-Marqui, & Cadaveira, 2008; McEvoy et al., 2001; Saliasi et al., 2013). Similarly, decreased P300 amplitude and increased latency have been consistently found with increasing memory load (for review see Kok, 2001; Polich, 2007). However, most studies reporting such results only involved young adult samples.

Although the above findings are promising with respect to the use of ERPs as a tool for assessing age-related effects on the neural processing underlying information encoding in WM, they are not conclusive. Therefore, the aim of the present study was to answer some questions in relation to the effects of aging on the time course of electrical brain activity associated with the self-initiated successful encoding of visual information in WM. The specific aims were to determine the following: i) whether there is an age-related slowing in the behavioral response to a memory task and in the ERP indexes of the cognitive processes involved in visual information encoding in WM; ii) whether such slowing is general or limited to the controlled processing of information to be encoded; iii) which stages of information encoding processing suffer an age-related reduction in allocation of processing resources; and iv) the effect of memory load and its interaction with age-related effects on task execution and in ERP components related to information encoding in WM.

For these purposes, ERPs were measured in a sample of healthy young and old adults while they performed a DMS task involving presentation of a stimulus that had to be memorized (encoding stage) without any specific instruction having been given about the strategy to use (i.e. through self-initiated strategies). Moreover, as the stimuli presented correspond to two different levels of memory load, the effects of any interaction between aging and memory load effects on electrical brain activity during information encoding in WM were able to be assessed.

II) METHODS AND MATERIALS

ii.1 Sample

The sample comprised 40 volunteers. All except three were right handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). All participants had normal or corrected-to-normal vision and reported no history of neurological or psychiatric disorders. In addition, all participants, none of whom were taking psychotropic medication, were instructed to abstain from consuming alcohol and caffeine the day before the experimental session. All volunteers gave their informed consent to participating in the study, and the study protocol was approved by the ethical Committee at the University of Santiago de Compostela (USC).

Participants were further divided in two groups (each with 16 females): 20 young adults (mean age = 23.85 ± 3.18 years) recruited from USC alumni, and 20 healthy old adults (mean age = 67.80 ± 7.69 years) recruited from USC courses for older adults and from two different cultural associations in which they participate in cognitively demanding activities (learning a foreign language, informatics courses, etc.). The two groups differ significantly in time spent in formal education (young: 16.25 ± 1.25 years, old: 14.12 ± 3.93 years; $t(18.79) = -2.160$, $p \leq .044$) but were equated in their scores on the Spanish version of the Wechsler Adults Intelligence Scale vocabulary subtest (Wechsler, 1997) (young: 47.95 ± 5.22, old: 48.15 ± 8.68; $t(31.41) = 0.89$, $p \leq .930$).

ii.2 Experimental protocol

Participants performed the visual DMS task illustrated in Figure 1, which is described in detail elsewhere (Pinal, Zurrón, & Díaz, 2014). After receiving brief training in the task, each participant completed a total of 200 trials divided in two blocks separated by an interval of 5 minutes. A warning tone (1000 Hz pitch, 50 ms duration) was used to indicate the start of each trial and was followed, 500 ms later, by presentation of a sample stimulus, which remained on the screen for 1000 ms. This was followed by a blank screen delay of 2500 or 5000 ms (50% of probability of appearance) and then by the presentation of three new dominoes as probe stimuli. The tiles remained on screen until the participants responded or for a maximum time of 3000 ms. The inter-trial interval duration was 800 ms. To minimize ocular artifacts, a fixation cross was placed in the center of the screen when no stimuli were presented. Stimuli presentation and response recording were controlled using Presentation® software (Neurobehavioral Systems, Inc., Albany, CA, USA).

For this study, only the sample stimulus was of interest as subjects had to encode this stimulus in WM. The sample stimulus was an adapted domino tile (length, 8 cm and width, 4 cm) comprising two vertically arranged white squares of equal size. The domino tiles were marked with between two and five black dots (1 cm in diameter) at the corners of each square, leaving with a gap of 1 cm between each dot and a gap of 0.5 cm between each dot and the edges of the squares. The domino tiles were presented on a black background in the center of a monitor (19", refresh rate of 100 Hz) located at a distance of 1 m from the participant's eyes, so that each domino subtended a visual angle of 4.58° x 2.28°.

Memory load was manipulated between trials by changing the number of dots on the dominoes, which were grouped into two memory load conditions: low load condition (LL) corresponding to dominoes with two or three dots, and a high load condition (HL) corresponding to dominoes with four or five dots. The first block of trials consisted of 90 low memory load trials, while the second block consisted of 110 high memory load trials. The percentage of repeated dominoes was maintained constant in both blocks (20%). The HL block included more trials than the LL block to ensure a good signal-to-noise ratio, since a higher proportion of errors was expected for this block.

The probe stimulus consisted of three dominoes with the same structure as the sample stimulus, and which also corresponded to the same memory load condition. These dominoes were presented simultaneously in the center of the monitor, and only one of them was identical to the sample stimulus (target). Participants were asked to identify the target as quickly and accurately as possible and to press the button corresponding to the position of the target on screen (left, center or right: this was counterbalanced across trials so it never appeared more than three consecutive trials in the same position) out of three response buttons arranged horizontally on a response device (Cedrus ®, model RB-530).

ii.3 EEG recordings and signal processing

During the experimental session, participants sat in a comfortable armchair inside a noise and light attenuated Faraday chamber. EEG activity was recorded at 51 active electrodes inserted in a cap and placed in the standard positions of the 10-10 system. Fronto-polar ground and nose tip reference were used, with all the electrode impedances maintained below 10 kΩ. EOG activity was also monitored with two electrodes placed at the outer canthi of both eyes (HEOG) and another two electrodes placed above and below the right eye (VEOG). The EEG signal was analogically filtered between 0.01 to 100 Hz, sampled at 500 Hz and digitally recorded for off-line analysis.

Recorded data were passed through a digital phase-shift free Butterworth filter with the high cut-off frequency at half power (-3 dB) set at 30 Hz (12 dB/octave roll-off), and with a low cut-off frequency at half power set at 0.1 Hz (12 dB/octave roll-off). A notch-filter centered at 50 Hz was also applied to avoid any contamination of electrical line noise. Ocular and muscular artifacts were corrected using the Infomax algorithm in an Independent Component Analysis (ICA) as implemented in Brain Vision Analyzer (v.2 Brain Products GmbH). Furthermore, a semi-automatic artifact rejection was conducted (i.e., trials with voltage changes of ±125 mV were excluded). Data was then segmented in epochs from 200 ms prior to sample stimulus presentation to 1000 ms post-stimulus, and baseline was corrected with the mean activity in the 200 ms prior to sample stimulus. Only epochs corresponding to correctly answered trials entered further analyses.

ii.4 Behavioral and electrophysiological data

The proportion of correct responses and reaction times (RTs) for the correctly responded trials were recorded for each participant and experimental condition (LL and HL).

As regards electrophysiological data, separate averaged ERP waveforms to sample stimulus were obtained for each memory load condition. The following components were identified: P1, N1, P2, N2 and P300. On the basis of the reports reviewed in the introduction section and by choosing the electrodes where amplitude was maximal, peak latency and baseline to peak amplitude of those components were measured as follows: the P1 component was considered the maximum peak at O1, Oz and O2 between 85 and 145

ms post-stimulus; N1 was defined as the most negative peak at P9, P7, P8, P10, between 150 and 210 ms post stimulus; the P2 component was measured as the largest positive peak at F3, Fz and F4 between 180 and 250 ms post-stimulus; N2 was considered the maximum negative-going peak in the trough between P2 and P300 positive waves at F3, Fz, F4, C3, Cz and C4 between 230 and 300 ms after sample stimulus onset; and P300 was identified as the maximum positive peak at P3, Pz and P4 between 300 and 500 ms post-stimulus. For each component latency and amplitude data were averaged across the selected electrodes. The statistical tests were applied to mean values for each component.

In addition, because the N2 component did not reach negative voltage values in the young participants, in contrast to the older participants (see Fig. 2); it was considered appropriate to measure N2 amplitude with respect to the previous and posterior positive peaks. In other words, in addition to the baseline to peak amplitude, the N2 amplitude was measured from peak to trough (P2-N2) and from trough to peak (N2-P300). These amplitude measures were made at the same electrodes as described earlier for N2. The mean amplitude across the selected electrodes was used in the statistical analysis.

Finally, as no ERP component peak was clearly identifiable from 500 ms after stimulus onset onwards, the mean amplitudes for three different time windows were obtained for frontal and parietal midline electrodes. The first time window spanned from 550 to 700 ms, the second one extended from 701 to 850 ms post-stimulus, and the final time window spanned from 851 to 1000 ms after stimulus onset.

ii.5 Statistical analyses

A mixed design analysis of variance (ANOVA) with Age Group (young and old) as the between subjects factor and Memory Load (LL and HL) as the within-subject factor was used to assess age related effects on behavioral performance (i.e., RTs and accuracy rates) in the visual DMS task, as well as their interactions with memory load effects.

Regarding brain electrical activity, mixed design ANOVAs, with Age Group (young and old) as the between subject factor and Memory Load (LL and HL) as the within subjects factor, were used to assess age related effects on the parameters (peak latency and amplitude values) of the ERP components and their possible modulation by memory load conditions. Two ANOVAs with the same structure were carried out with the amplitude values of P2-N2 and N2-P300.

Mixed design ANOVAs, with Age Group (young and old) as the between subjects factor and both Memory Load (LL and HL) and Region (frontal and parietal) as within subjects factors, were also applied to amplitude values in the time intervals 550-700, 701-850 y 851-1000 ms post-stimulus.

For all ANOVAs performed in the present work, Greenhouse-Geisser correction was applied whenever the sphericity assumption was violated, and Bonferroni adjustment was used to correct for multiple comparisons.

Finally, to assess the relationship between electrical brain activity and behavioral performance independently of age (specifically, to determine which neural processes at encoding were related to task execution), partial correlation analysis controlling for age (Amenedo, Lorenzo-López, & Pazo-Alvarez, 2012; Finnigan et al., 2011) was executed between behavioral outputs (RTs and accuracy rates) and latency or amplitude values of the ERP components. Behavioral outputs and ERP parameters were averaged across load conditions prior to being entered in the partial correlation analyses. Bootstrapping (1000 samples) was used to control for multiple comparisons.

Pearson's correlations were also calculated separately for each age group between the behavioral outputs and the ERP components parameters that were significantly correlated when age was partialled out.

In all statistical tests, differences were considered statistically significant at $p \leq .05$.

III) RESULTS

iii.1 Behavioral performance

The ANOVAs of task performance data (i.e., accuracy rates and RTs) revealed a significant effect for Age Group factor in both measures ([$F(1,38)=24.73$, $p<0.001$] and [$F(1,38)=59.04$, $p<0.001$], respectively). Therefore, old adults showed significantly lower accuracy rates and significantly longer RT relative to young adults (Table 1).

In addition, the interaction between the factors Age Group and Memory Load also had a statistically significant effect on accuracy rates [$F(1,38)=16.32$, $p<0.001$], with significantly lower accuracy rates in the HL than the LL condition only in the old adults group ($p<0.001$).

iii.2 Electrical brain activity

For P1 and N1 amplitude and latency, the ANOVAs did not reveal any significant effect of Age Group, Memory Load or of their interaction.

Regarding the P2 component, a main effect of Age Group was found for its latency [$F(1,38)=6.36$, $p\leq0.016$] and amplitude [$F(1,38)=7.79$, $p\leq0.008$]. Thus, the P2 latency was significantly longer in the old adults than in the young adults, while amplitude was significantly lower in old adults than in the young adults (Fig. 2).

The Age Group factor also had a significant effect on N2 latency [$F(1,38)=8.19$, $p\leq0.007$] and amplitude [$F(1,38)=11.71$, $p\leq0.002$]. The latency of N2 was significantly longer and the N2 amplitude was significantly larger in the older adults than in the young participants (Fig.2). However, P2-N2 and N2-P300 peak to peak amplitudes were not significantly affected by the factor Age Group. No significant effects were observed for Memory Load factor or the interaction between Memory Load and Age Group on N2 peak latency or amplitude, or on P2-N2 and N2-P300 peak to peak amplitudes.

Regarding the P300 component, latency values did not differ significantly between the two age groups, although as can be seen in Table 2, old adults presented longer latencies than young adults. Regarding the P300 amplitude, there was a main effect of Age Group [$F(1,38)=15.43$, $p<0.001$], with significantly lower amplitude in the old adults than in the young adults (Fig. 2). Neither Memory Load factor nor its interaction with Age Group had statistically significant effects on P300 latency and amplitude.

Finally, the ANOVAs revealed that Age Group had a main effect on mean amplitude in the 550-700 ms interval [$F(1,38)=7.21$, $p\leq0.011$], when amplitude was significantly lower in old than young adults. In the 701-850 ms and 851-1000 ms time intervals, a main effect of Memory Load was found [$F(1,38)=13.01$, $p\leq0.001$ and $F(1,38)=14.37$, $p\leq0.001$, respectively], with significantly larger mean amplitudes in the HL condition than in the LL trials in both cases (Fig. 2).

iii.3 Relationships between electrical brain activity and behavioral performance

Regarding partial correlation analysis, once the effects of age (chronological) were controlled for, a significant relationship between accuracy rates and N2 latency emerged ($r = .452$, $p\leq.004$) (Fig. 3). Thus, the accuracy rates increased with N2 latency.

However, after examination of the scatterplot, we decided to calculate Pearson's correlations between N2 latency and accuracy rates separately for each age Group. These tests revealed a significant correlation between accuracy rates and N2 latency only in the older adults ($r = .512$, $p\leq.021$) (Fig.3).

IV) DISCUSSION

iv.1 Task performance

Results revealed age-related differences in performance of the experimental task, as the response of the old participants to the DMS task were less effective (lower accuracy rates) and slower (longer RTs) than those of young adults. In addition, memory load was found to modulate task performance, but only in the old adults, who showed lower accuracy rates when memory load was high than when it was low. The latter result may indicate that old adults are more sensitive than young adults to memory load effects.

iv.2 Electrical brain activity related to information encoding in WM

iv.2.1 ERP latency measures and slowing of processing speed

Analysis of brain electrical activity during visual information encoding in WM showed that P1, N1 and P300 latencies were not affected by age or memory load. On the other hand, P2 and N2 latencies were longer in old than in young participants, but were not modulated by memory load.

In contrast with the findings of previous studies that used Sternberg or DMS tasks (Finnigan et al., 2011; Gazzaley et al., 2008; Zanto et al., 2010), there were no differences between old and young adults for P1 and N1 latencies. These components are usually associated with perceptual processing of visual inputs (Itier & Taylor, 2004; Kok, 1997; Luck, 2012; Taylor, 2002; Vogel & Luck, 2000); consequently, differences between the present and previous studies in the type (domino tiles vs words, faces or a circular aperture of 290 colored dots), number (one domino tile vs 4 to 8 words, 2 faces or 2 circular apertures of colored dots) and/or on the presentation of stimuli (simultaneous vs sequential) may explain the discrepancy in the results. Nevertheless, the present results indicate that the age-related slowing of processing speed does not affect perceptual processing of stimuli to be encoded, at least under the experimental conditions used in the present study.

As regards P2 and N2 components, longer latencies were observed for old than for young adults, which is consistent with findings from previous studies that used n-back tasks (Missonnier et al., 2004, 2011). Despite the lack of general agreement about its functional role, P2 has been related to a top-down mechanism for rapid evaluation of stimulus significance that facilitates the posterior processing of familiar (M. S. James, Johnstone, & Hayward, 2001; Paynter, Reder, & Kieffaber, 2009) or subjectively relevant stimuli (Gilmore, Clementz, & Berg, 2009; Potts & Tucker, 2001; Potts, 2004; Schapkin, Gusev, & Kuhl, 2000). Moreover, N2 has been considered a correlate of the ease of visual information encoding (Ferrari, Bradley, Codispoti, & Lang, 2010; Nittono, Shibuya, & Hori, 2007); and its latency has been used as a physiological marker of the timing of access to different properties of a stimulus (Folstein & van Petten, 2008; Schmitt, Münte, & Kutas, 2000; Schmitt, Rodriguez-Fornells, Kutas, & Münte, 2001; Schmitt, Schiltz, Zaake, Kutas, & Münte, 2001). Therefore, the present results appear to indicate that in situations like those established in the present study, there is an age-related slowing in stimulus analysis and evaluation during information encoding in WM.

No significant age-related differences were found for P300 latency, which contradicts the results of previous studies (for reviews see Polich, 1996; Friedman, 2012). Nonetheless, P300 latencies were longer in older adults than in young adults, especially in the HL condition (Table 2). The fact that in old adults the P300 resembled a plateau with multiple peaks (see Figure 2) and that the latency was measured only from the most positive peak may explain the lack of significant differences between both groups.

In summary, the results for ERPs latency showed that the age-related slowing of processing speed is not general during information encoding in WM, since it did not affect initial perceptual processing of the stimulus, but affected processes related to stimulus analysis and evaluation of stimulus features. In addition, during information encoding, memory load did not modulate the latency of the ERP components under study.

iv.2.2 ERP amplitude measures and allocation of processing resources

With respect to the amplitude of the ERP components, no significant effects of age or memory load were found for P1 or N1. However, the analyses revealed lower P2 and P300 amplitudes as well as lower mean amplitude in the 550-700 ms time interval for old than young adults. Moreover, mean amplitudes in 701-850 ms and 851-1000 ms time intervals were significantly larger in high than load memory load conditions in both age groups.

The lack of significant age-related effects on P1 and N1 amplitudes contrasts with previous findings for these components, which have been associated with perceptual analysis of visual inputs (e.g. Gazzaley et al., 2008; Zanto et al., 2010; Finnigan et al., 2011). This is probably due to differences in the type, number or presentation of stimuli used in this and previous studies. Overall, the results of the present study appear to indicate that under the conditions imposed by the present task, differences in the allocation of processing resources for perceptual processing during visual information encoding in WM are not related to age.

Previous studies concerning aging effects on P2 amplitude showed partly opposite results (McEvoy et al., 2001; Missonnier et al., 2004, 2011). The amplitude of this component, which has itself been repeatedly related to some aspects of stimulus evaluation, has been associated with the amount of processing resources allocated to a rapid top-down evaluation of stimulus significance (Wang, Song, Qu, & Ding, 2010). Hence, the lower P2 amplitude found for old than young adults in the present study might indicate an age-related deficit in the allocation of processing resources for the evaluation of stimulus significance.

The N2 peak amplitude was significantly larger in the old than the young group, although P2-N2 and N2-P300 peak to peak amplitudes were not affected by age. Consequently, it appears that age group differences in N2 peak amplitude are driven by the large positive amplitude that P2 and P300 had in the young adults, which, in turn, produce more positive (above baseline) N2 amplitude values for young than old adults.

Previous studies have consistently found an age-related reduction in the amplitude of P300 component at parietal electrodes (McEvoy et al., 2001; Saliasi et al., 2013; for a review see Polich, 1996; Friedman, 2012). This has been interpreted as an age-related decrease in the processing resources available for allocation to stimulus categorization. Likewise, in the present study, the P300 amplitude was lower in old than in young participants, and mean amplitude was also lower in the 550-700 ms time interval, which immediately follows P300 peak. Therefore, the present results provide evidence that, relative to young adults, old adults have lower amounts of processing resources available for the successful categorization of stimuli to be encoded in WM.

Memory load effects were restricted to the mean amplitude for 701-850 ms and 851-1000 ms time intervals, during which mean amplitudes were significantly larger for high

load than low load stimuli. These results are consistent with those of García-Larrea and Cézanne-Bert (1998), who interpreted the larger amplitude under high load conditions as an index of extra stimulus processing that is not needed in low load conditions. Furthermore, ERP activity following P300 has been related to active maintenance processes and/or to elaboration of categorized and encoded materials in WM (A. Chen et al., 2007; Folstein & van Petten, 2011; García-Larrea & Cézanne-Bert, 1998). Thus, it seems that the memory load manipulations in the present study did not interact with age effects on electrical brain activity. However, high memory load may require the allocation of extra processing resources for mental processes once the target stimulus has been categorized and has to be maintained in an active state in WM for its comparison with the probe stimulus.

It is noteworthy that in the present study no memory load effects were found on electrical brain activity before 700 ms. This is at odds with the findings of previous studies in which memory load was manipulated during information encoding in WM (e.g. Morgan et al., 2008; Soria Bauser et al., 2011). The previous studies reported an increase in P1 and decrease in N1 amplitude (Morgan et al., 2008), as well as memory load dependent P300 amplitude reductions during the encoding stage of DMS tasks (Morgan et al., 2008; Soria Bauser et al., 2011). Differences between the present and previous results may depend on how memory load was manipulated (i.e., number of dots inside a single item vs number of items to be encoded). Consequently, in the present study, memory load manipulation (total number of dots on a domino tile) was not sufficient to impose great demands on perceptual processing as well as on stimulus evaluation and categorization cognitive processes. This is supported by the very high accuracy rates for task performance in young adults (close to 95% in both memory load conditions).

In summary, analysis of the amplitude of ERP components revealed that the amount of processing resources allocated to perceptual processing is preserved in old adults; however, there is a decrease in the availability of processing resources for the evaluation and categorization of visual stimuli to be encoded in WM. Moreover, in both age groups high memory load conditions require allocation of processing resources for extra processing after target stimulus categorization has been completed, when maintenance of information in WM and rehearsal processes are carried out.

iv.3 Relation between brain activity and task performance

Partial correlation analysis between the latency or amplitude of ERP components and task performance measures, with age partialled out, showed that brain electrical activity during information encoding in WM is related to DMS task performance. In particular, N2 latency was directly related to accuracy rates. Therefore, higher accuracy rates were associated with longer the N2 latencies. In other words, the longer the time dedicated to feature analysis for the stimuli to be encoded in WM, the better the recognition of those stimuli when presented among two other similar stimuli that acted as distractors.

However, visual inspection of the scatterplot, in which the effect seems to be driven by the data for old adults, prompted us to calculate the Pearson's correlation between N2 latency and accuracy rates for each group separately. It seems that in the old age group, long evaluation of stimulus features is more beneficial than in young adults. Overall, the results of the correlation analyses might indicate that the longer the time spent in stimulus feature analysis during encoding of information in WM, the better the accuracy rates in a DMs task, especially in old adults.

V) CONCLUSION

The aim of the present study was to evaluate the effect of normal aging on the successful self-initiated encoding of information in WM, as well as to determine the potential interactions between aging and memory load effects. The results showed that high levels of memory load caused a decline in task performance only in old participants. Nevertheless, memory load effects on brain electrical activity were age independent and characterized by an increase in processing resources allocated for information maintenance in WM once the stimulus has been categorized. Regarding normal aging effects, the results revealed an age-related slowing in the response to the memory task and that the age-related slowing of processing speed is not general, since target stimulus analysis and evaluation processes are slower, but perceptual processing is not. The findings also indicated an age dependent decline in the allocation of processing resources for stimulus evaluation and categorization. Finally, correlation analyses showed that brain electrical activity during information encoding in WM is related to task performance. In particular, longer N2 latencies, which are associated with stimulus analysis and evaluation processes, predicted higher accuracy rates in the DMS task, especially in old adults.

VI) ACKNOWLEDGEMENTS

This study was funded by the Spanish Government through the Ministerios de Educación (BES 2008-005929) and Economía y Competitividad (PSI2010-22224-C03-03) and by the Galician Government through the Consellería de Economía e Industria (10 PXIB 211070 PR), and Consellería de Educación e Ordenación Universitaria (Axudas para a Consolidación e Estruturación de unidades de investigación competitivas do sistema universitario de Galicia. Ref: CN 2012/033).

VII) CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

VIII) AUTHORS AND CONTRIBUTORS

All three authors contributed to the design and planning of the present study and also cooperated in writing the manuscript. Diego Pinal was in charge of data acquisition and analysis.

IX) REFERENCES

Amenedo, E., Lorenzo-López, L., and Pazo-Alvarez, P. (2012). Response processing during visual search in normal aging: the need for more time to prevent cross talk between spatial attention and manual response selection. *Biol. Psychol.* 91, 201–211. doi:10.1016/j.biopsycho.2012.06.004.

Baddeley, A. (2012). Working Memory: Theories, Models, and Controversies. *Annu. Rev. Psychol.* 63, 12.1–12.29. doi:10.1146/annurev-psych-120710-100422.

Baddeley, A. D., and Hitch, G. (1974). Working Memory. *Psychol. Learn. Motiv.* 8, 47–89. doi:10.1016/S0079-7421(08)60452-1.

Baltes, P. B., Staudinger, U. M., and Lindenberger, U. (1999). Lifespan psychology: theory and application to intellectual functioning. *Annu. Rev. Psychol.* 50, 471–507. doi:10.1146/annurev.psych.50.1.471.

Buckner, R. L. (2004). Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron* 44, 195–208. doi:10.1016/j.neuron.2004.09.006.

Cabeza, R., and Dennis, N. A. (2013). "Frontal lobes and aging: Deterioration and Compensation," in *Principles of Frontal Lobe Function*, eds. D. T. Stuss and R. T. Knight (New York: Oxford University Press, USA), 628–652. doi:10.1093/acprof:oso/9780195134971.001.0001.

Chen, A., Luo, Y., Wang, Q., Yuan, J., Yao, D., and Li, H. (2007). Electrophysiological correlates of category induction: PSW amplitude as an index of identifying shared attributes. *Biol. Psychol.* 76, 230–238. doi:10.1016/j.biopsycho.2007.08.007.

Craik, F. I. M., and Rose, N. S. (2012). Memory encoding and aging: a neurocognitive perspective. *Neurosci. Biobehav. Rev.* 36, 1729–1739. doi:10.1016/j.neubiorev.2011.11.007.

Fabiani, M. (2012). It was the best of times, it was the worst of times: a psychophysiologist's view of cognitive aging. *Psychophysiology* 49, 283–304. doi:10.1111/j.1469-8986.2011.01331.x.

Ferrari, V., Bradley, M. M., Codispoti, M., and Lang, P. J. (2010). Detecting novelty and significance. *J. Cogn. Neurosci.* 22, 404–411. doi:10.1162/jocn.2009.21244.

Finnigan, S., O'Connell, R. G., Cummins, T. D. R., Broughton, M., and Robertson, I. H. (2011). ERP measures indicate both attention and working memory encoding decrements in aging. *Psychophysiology* 48, 601–611. doi:10.1111/j.1469-8986.2010.01128.x.

Folstein, J. R., and van Petten, C. (2011). After the P3: late executive processes in stimulus categorization. *Psychophysiology* 48, 825–841. doi:10.1111/j.1469-8986.2010.01146.x.

Folstein, J. R., and van Petten, C. (2008). Influence of cognitive control and mismatch on the N2 component of the ERP: a review. *Psychophysiology* 45, 152–170. doi:10.1111/j.1469-8986.2007.00602.x.

Friedman, D. (2012). "The components of aging," in *Oxford Handbook of event-related potential components*, eds. S. J. Luck and E. S. Kappenman (New York: Oxford University Press), 513–536.

Friedman, D., Nessler, D., and Johnson Jr, R. (2007). Memory encoding and retrieval in the aging brain. *Clin. EEG Neurosci.* 38, 2–7. doi:10.1177/155005940703800105.

García-Larrea, L., and Cézanne-Bert, G. (1998). P3, positive slow wave and working memory load: a study on the functional correlates of slow wave activity. *Electroencephalogr. Clin. Neurophysiol.* 108, 260–273. doi:10.1016/S0168-5597(97)00085-3.

Gazzaley, A., Clapp, W. C., Kelley, J., McEvoy, K., Knight, R. T., and D'Esposito, M. (2008). Age-related top-down suppression deficit in the early stages of cortical visual memory processing. *Proc. Natl. Acad. Sci. U. S. A.* 105, 13122–13126. doi:10.1073/pnas.0806074105.

Gazzaley, A., Sheridan, M. A., Cooney, J. W., and D'Esposito, M. (2007). Age-related deficits in component processes of working memory. *Neuropsychology* 21, 532–539. doi:10.1037/0894-4105.21.5.532.

Gilmore, C. S., Clementz, B. A., and Berg, P. (2009). Hemispheric differences in auditory oddball responses during monaural versus binaural stimulation. *Int. J. Psychophysiol.* 73, 326–333. doi:10.1016/j.ijpsycho.2009.05.005.

Glisky, E. L. (2007). "Changes in cognitive function in human aging," in *Brain aging: models, methods, and mechanisms*, ed. D. R. Riddle (Boca Ratón (FL): CRC Press), 3–20. doi:10.1201/9781420005523.sec1.

Hasher, L., and Zacks, R. T. (1988). Working Memory, Comprehension, & Aging: A review and new view. *Psychol. Learn. Motiv.* 22, 193–225. doi:10.1016/S0079-7421(08)60041-9.

Hashtroudi, S., Parker, E. S., Luis, J. D., and Reisen, C. A. (1989). Generation and elaboration in older adults. *Exp. Aging Res.* 15, 73–78. doi:10.1080/03610738908259760.

Itier, R. J., and Taylor, M. J. (2004). N170 or N1? Spatiotemporal Differences between Object and Face Processing Using ERPs. *Cereb. Cortex* 14, 132–142. doi:10.1093/cercor/bhg111.

James, M. S., Johnstone, S. J., and Hayward, W. G. (2001). Event-Related Potentials, Configural Encoding, and Feature-Based Encoding in Face Recognition. *J. Psychophysiol.* 15, 275–285. doi:10.1027//0269-8803.15.4.275.

John, E. R., Easton, P., Isenhart, R., Allen, P., and Gulyashar, A. (1996). Electrophysiological analysis of the registration, storage and retrieval of information in delayed matching from samples. *Int. J. Psychophysiol.* 24, 127–144. doi:10.1016/S0167-8760(96)00056-6.

Jonides, J., Lewis, R. L., Nee, D. E., Lustig, C. A., Berman, M. G., and Sledge Moore, K. (2008). The mind and brain of short-term memory. *Annu. Rev. Psychol.* 59, 193–224. doi:10.1146/annurev.psych.59.103006.093615.

Kalkstein, J., Checksfield, K., Bollinger, J., and Gazzaley, A. (2011). Diminished top-down control underlies a visual imagery deficit in normal aging. *J. Neurosci.* 31, 15768–15774. doi:10.1523/JNEUROSCI.3209-11.2011.

Kok, A. (1997). Event-related-potential (ERP) reflections of mental resources: a review and synthesis. *Biol. Psychol.* 45, 19–56. doi:10.1016/S0301-0511(96)05221-0.

Kok, A. (2001). On the utility of P3 amplitude as a measure of processing capacity. *Psychophysiology* 38, 557–577. doi:10.1017/S0048577201990559.

Lorenzo-López, L., Amenedo, E., Pascual-Marqui, R. D., and Cadaveira, F. (2008). Neural correlates of age-related visual search decline: a combined ERP and sLORETA study. *Neuroimage* 41, 511–524. doi:10.1016/j.neuroimage.2008.02.041.

Luck, S. J. (2012). "Event-related Potentials," in *APA handbook of research methods in psychology: Foundations, planning, measures and psychometrics*, eds. H. Cooper, P. M. Camic, D. L. Long, A. T. Panter, D. Rindskopf, and K. J. Sher (Washington, DC: American Psychological Association), 523–546. doi:10.1037/13619-028.

McEvoy, L. K., Pellouchoud, E., Smith, M. E., and Gevins, A. (2001). Neurophysiological signals of working memory in normal aging. *Cogn. Brain Res.* 11, 363–376. doi:10.1016/S0926-6410(01)00009-X.

Missonnier, P., Gold, G., Leonards, U., Costa-Fazio, L., Michel, J.-P., Ibáñez, V., and Giannakopoulos, P. (2004). Aging and working memory: early deficits in EEG activation of posterior cortical areas. *J. Neural Transm.* 111, 1141–1154. doi:10.1007/s00702-004-0159-2.

Missonnier, P., Herrmann, F. R., Rodriguez, C., Deiber, M.-P., Millet, P., Fazio-costa, L., Gold, G., and Giannakopoulos, P. (2011). Age-related differences on event-related potentials and brain rhythm oscillations during working memory activation. *J. Neural Transm.* 118, 945–955. doi:10.1007/s00702-011-0600-2.

Morgan, H. M., Klein, C., Boehm, S. G., Shapiro, K. L., and Linden, D. E. J. (2008). Working memory load for faces modulates P300, N170, and N250r. *J. Cogn. Neurosci.* 20, 989–1002. doi:10.1162/jocn.2008.20072.

Nittono, H., Shibuya, Y., and Hori, T. (2007). Anterior N2 predicts subsequent viewing time and interest rating for novel drawings. *Psychophysiology* 44, 687–696. doi:10.1111/j.1469-8986.2007.00539.x.

Oberauer, K., and Kliegl, R. (2001). Beyond resources: Formal models of complexity effects and age differences in working memory. *Eur. J. Cogn. Psychol.* 13, 187–215. doi:10.1080/09541440042000278.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113. doi:10.1016/0028-3932(71)90067-4.

Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N. S., Smith, A. D., and Smith, P. K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychol. Aging* 17, 299–320. doi:10.1037//0882-7974.17.2.299.

Park, D. C., and Reuter-Lorenz, P. A. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annu. Rev. Psychol.* 60, 173–196. doi:10.1146/annurev.psych.59.103006.093656.

Paxton, J. L., Barch, D. M., Racine, C. A., and Braver, T. S. (2008). Cognitive control, goal maintenance, and prefrontal function in healthy aging. *Cereb. cortex* 18, 1010–1028. doi:10.1093/cercor/bhm135.

Paynter, C. A., Reder, L. M., and Kieffaber, P. D. (2009). Knowing we know before we know: ERP correlates of initial feeling-of-knowing. *Neuropsychologia* 47, 796–803. doi:10.1016/j.neuropsychologia.2008.12.009.

Pinal, D., Zurrón, M., and Díaz, F. (2014). Effects of load and maintenance duration on the time course of information encoding and retrieval in working memory: from perceptual analysis to post-categorization processes. *Front. Hum. Neurosci.* 8, Article 165. doi:10.3389/fnhum.2014.00165.

Polich, J. (1996). Meta-analysis of P300 normative aging studies. *Psychophysiology* 33, 334–353. doi:10.1111/j.1469-8986.1996.tb01058.x.

Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. *Clin. Neurophysiol.* 118, 2128–2148. doi:10.1016/j.clinph.2007.04.019.

Potts, G. F. (2004). An ERP index of task relevance evaluation of visual stimuli. *Brain Cogn.* 56, 5–13. doi:10.1016/j.bandc.2004.03.006.

Potts, G. F., and Tucker, D. M. (2001). Frontal evaluation and posterior representation in target detection. *Cogn. Brain Res.* 11, 147–156. doi:10.1016/S0926-6410(00)00075-6.

Rousselet, G. A., Husk, J. S., Pernet, C. R., Gaspar, C. M., Bennett, P. J., and Sekuler, A. B. (2009). Age-related delay in information accrual for faces: evidence from a parametric, single-trial EEG approach. *BMC Neurosci.* 10, 114. doi:10.1186/1471-2202-10-114.

Saliasi, E., Geerligs, L., Lorist, M. M., and Maurits, N. M. (2013). The Relationship between P3 Amplitude and Working Memory Performance Differs in Young and Older Adults. *PLoS One* 8, e63701. doi:10.1371/journal.pone.0063701.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychol. Rev.* 103, 403–428. doi:10.1037/0033-295X.103.3.403.

Schapkin, S. A., Gusev, A. N., and Kuhl, J. (2000). Categorization of unilaterally presented emotional words: an ERP analysis. *Acta Neurobiol. Exp. (Wars).* 60, 17–28.

Schmitt, B. M., Münte, T. F., and Kutas, M. (2000). Electrophysiological estimates of the time course of semantic and phonological encoding during implicit picture naming. *Psychophysiology* 37, 473–484. doi:10.1017/S0048577200981782.

Schmitt, B. M., Rodriguez-Fornells, A., Kutas, M., and Münte, T. F. (2001a). Electrophysiological estimates of semantic and syntactic information access during tacit picture naming and listening to words. *Neurosci. Res.* 41, 293–298. doi:10.1016/S0168-0102(01)00286-3.

Schmitt, B. M., Schiltz, K., Zaake, W., Kutas, M., and Münte, T. F. (2001b). An electrophysiological analysis of the time course of conceptual and syntactic encoding during tacit picture naming. *J. Cogn. Neurosci.* 13, 510–522. doi:10.1162/08989290152001925.

Soria Bauser, D. A., Mayer, K., Daum, I., and Suchan, B. (2011). Encoding/retrieval dissociation in working memory for human body forms. *Behav. Brain Res.* 220, 65–73. doi:10.1016/j.bbr.2011.01.032.

Sternberg, S. (1966). High-speed scanning in human memory. *Science (80-.).* 153, 652–654. doi:10.1126/science.153.3736.652.

Taylor, M. J. (2002). Non-spatial attentional effects on P1. *Clin. Neurophysiol.* 113, 1903–1908. doi:10.1016/S1388-2457(02)00309-7.

Vogel, E. K., and Luck, S. J. (2000). The visual N1 component as an index of a discrimination process. *Psychophysiology* 37, 190–203. doi:10.1111/1469-8986.3720190.

Wang, Y., Song, Y., Qu, Z., and Ding, Y. (2010). Task difficulty modulates electrophysiological correlates of perceptual learning. *Int. J. Psychophysiol.* 75, 234–240. doi:10.1016/j.ijpsycho.2009.11.006.

Wechsler, D. (1997). Wechsler Adult Intelligence Scale—Third edition.

West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychol. Bull.* 120, 272–292. doi:10.1037/0033-2909.120.2.272.

Zanto, T. P., Toy, B., and Gazzaley, A. (2010). Delays in neural processing during working memory encoding in normal aging. *Neuropsychologia* 48, 13–25. doi:10.1016/j.neuropsychologia.2009.08.003.

TABLES

Table 1. *Behavioral data***.** Reaction time (in milliseconds) and percentage accuracy for each group and memory load condition. Mean value ± standard deviation.

	OLD		YOUNG	
	LOW LOAD	HIGH LOAD	LOW LOAD	HIGH LOAD
REACTION TIME	1530.1 ± 208.8	1668.2 ± 175.6	1079.8 ± 208.7	1187.8 ± 220.3
ACCURACY	89.9 ± 8.9	78.8 ± 13.1	96.9 ± 3.2	93.7 ± 3.7

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Table 2. *Parameters of ERP components*. Latency (in milliseconds) and amplitude (in μV) for each group and memory load condition. Mean value ± standard error.

		OLD		YOUNG	
		LOW LOAD	HIGH LOAD	LOW LOAD	HIGH LOAD
P1	*Latency*	121.7 ± 3.2	120.8 ± 3.8	117.7 ± 2.3	115.6 ± 2.8
	Amplitude	5.3 ± 0.9	4.6 ± 0.8	6.3 ± 0.9	7.0 ± 1.0
N1	*Latency*	175.9 ± 3.4	174.7 ± 3.3	167.2 ± 3.5	170.4 ± 3.2
	Amplitude	-1.7 ± 0.5	-1.6 ± 0.6	-1.4 ± 0.7	-1.1 ± 0.6
P2	*Latency*	220.6 ± 3.9	218.0 ± 4.0	208.5 ± 4.5	204.1 ± 3.4
	Amplitude	2.9 ± 0.8	3.2 ± 0.8	5.9 ± 0.6	5.6 ± 0.6
N2	*Latency*	287.6 ± 4.4	289.1 ± 5.9	270.7 ± 2.9	275.7 ± 3.5
	Amplitude	-1.4 ± 0.8	-0.7 ± 0.7	2.2 ± 0.7	2.4 ± 0.7
P3	*Latency*	422.8 ± 10.5	414.6 ± 12.4	401.0 ± 10.7	402.9 ± 9.0
	Amplitude	2.2 ± 0.8	3.0 ± 0.6	7.8 ± 1.1	7.5 ± 1.2
550-700 ms	*Fz Amplitude*	-0.5 ± 0.6	0.3 ± 0.6	2.5 ± 0.9	3.2 ± 0.9
	Pz Amplitude	0.2 ± 0.6	1.4 ± 0.6	3.4 ± 1.1	3.4 ±1.2
701-850 ms	*Fz Amplitude*	-0.8 ± 0.8	0.1 ± 0.7	1.0 ± 0.8	2.3 ± 0.8
	Pz Amplitude	-0.7 ± 0.8	0.7 ± 0.7	0.6 ± 1.0	2.4 ± 1.3
851-1000 ms	*Fz Amplitude*	-1.2 ± 0.9	-0.0 ±0.8	0.7 ± 0.8	1.9 ± 0.8
	Pz Amplitude	-1.9 ± 0.9	-0.2 ± 0.7	-0.3 ± 0.9	1.4 ± 1.2

FIGURE LEGENDS

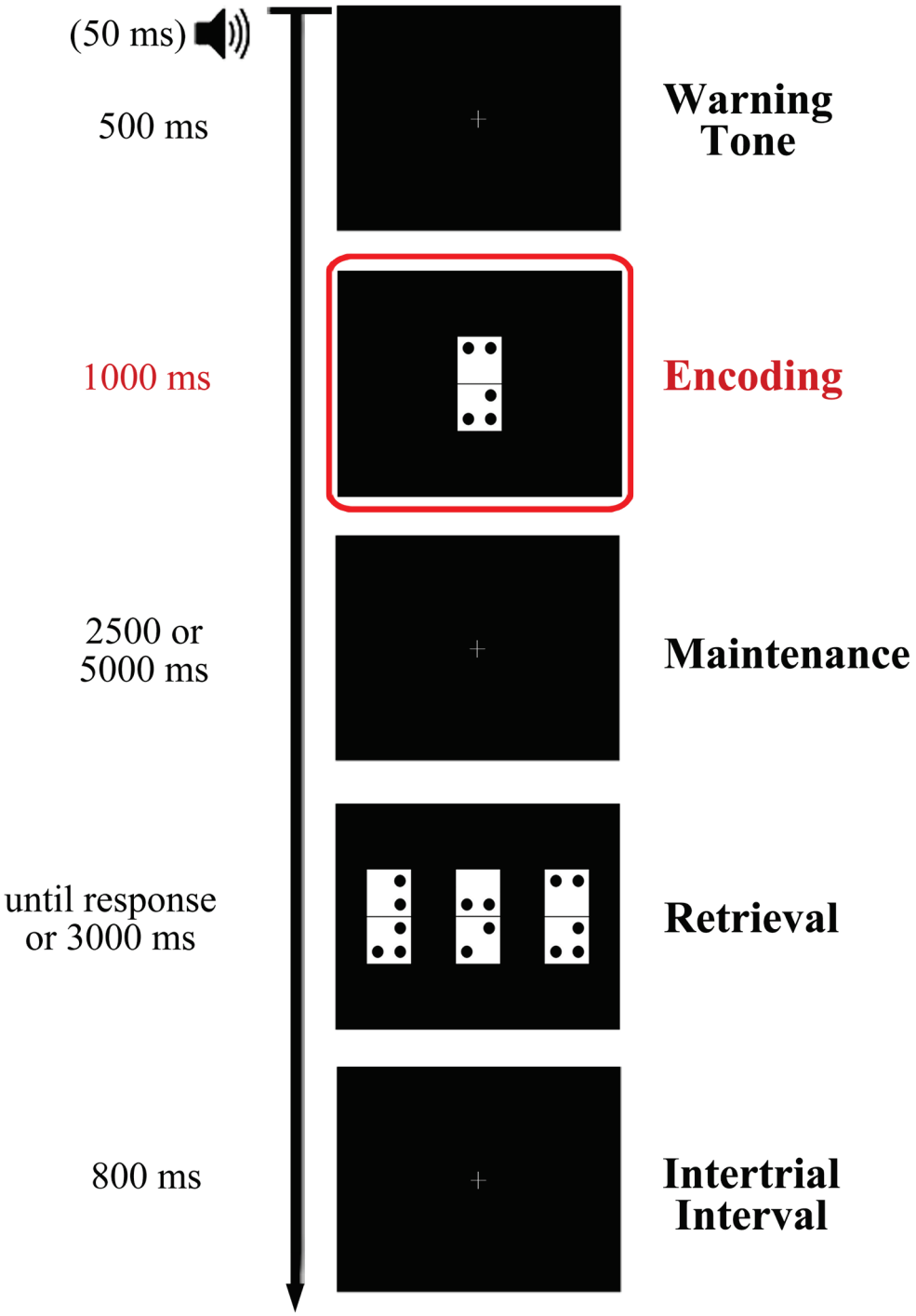
Fig. 1 Diagram of the delayed match to sample task used in the study. Participants were presented with a domino tile, the configuration of which they had to hold in mind for a variable delay (2.5 or 5 s) before identifying it as quickly and accurately as possible from among three different options presented simultaneously at the retrieval stage. The encoding phase, which was the focus of the present study, is highlighted in red.

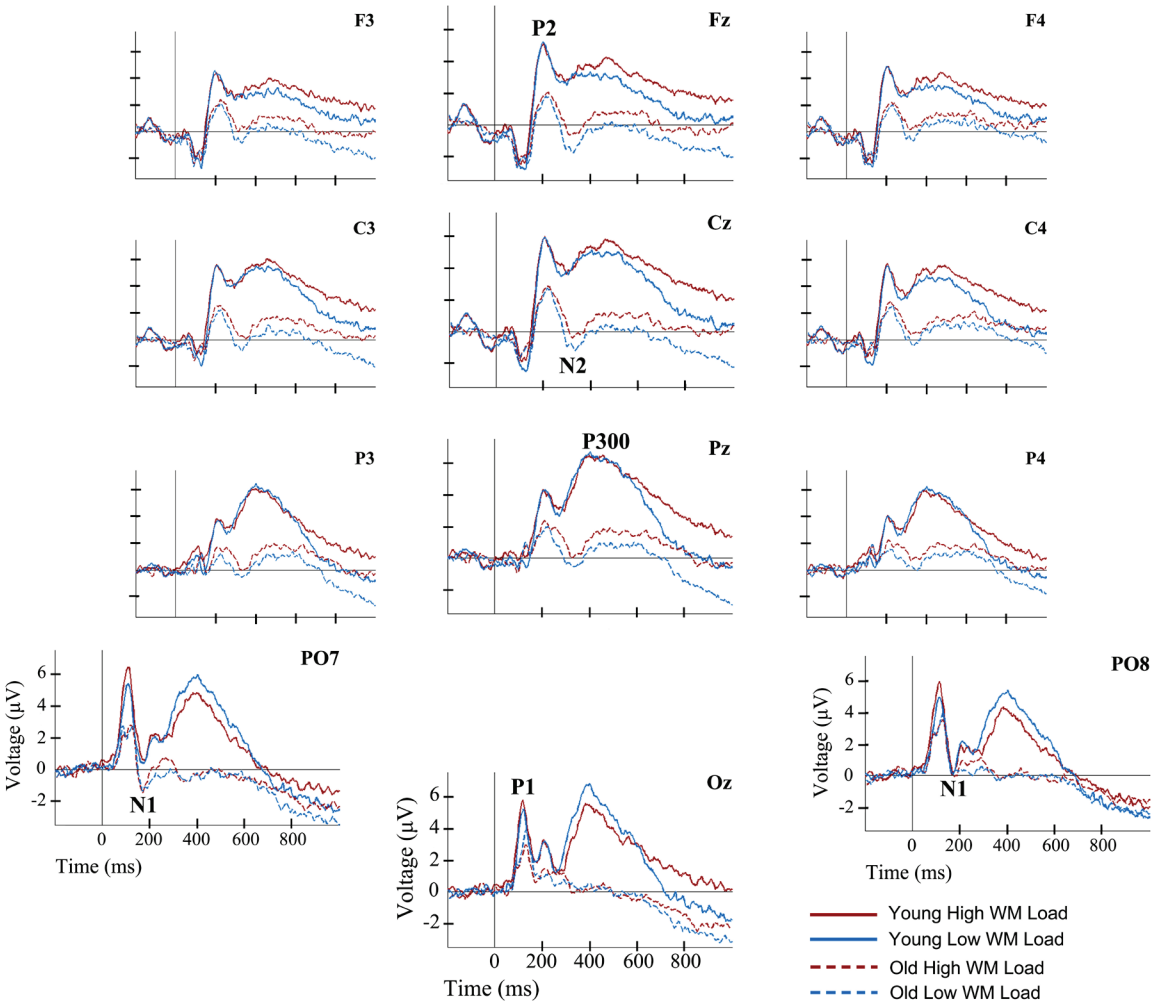
Fig 2. ERP waveforms for young and old groups, and for two load conditions, at several electrode locations during information encoding in WM. Solid lines represent the ERP waveforms of young adults during encoding of information in WM. Dashed lines depict the ERP waveforms of old adults during information encoding in WM. Red lines correspond to the HL condition. Blue lines correspond to the LL condition.

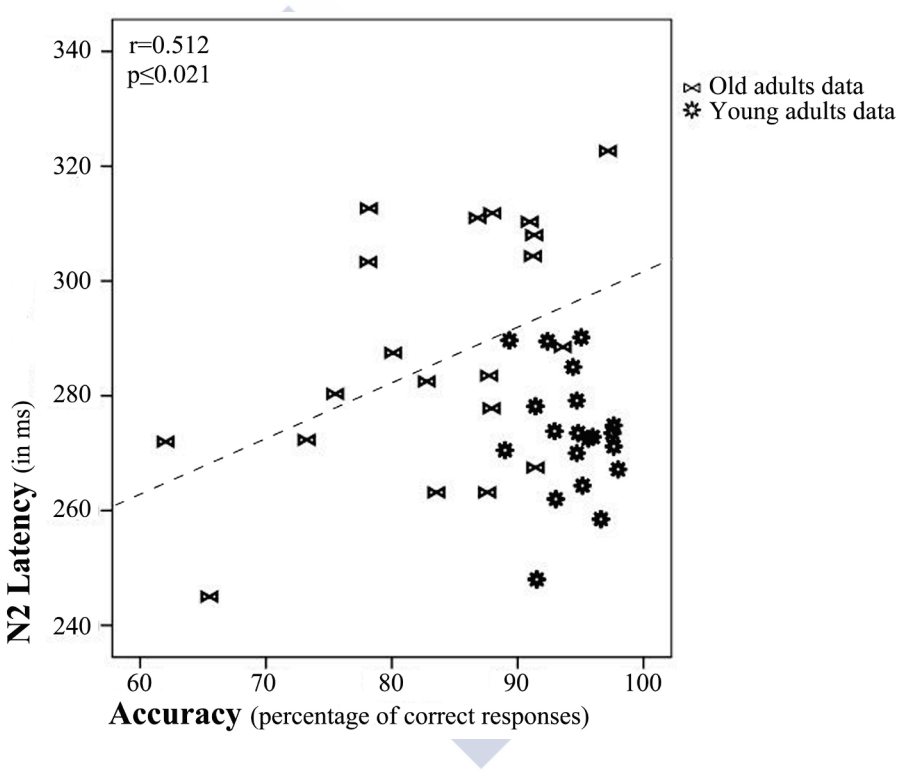
Fig 3. Relation between N2 latency and accuracy rates. Scatterplot of data for young and old adults. The depicted best fit line and correlation values (r and associated p) refer to Pearson's correlation analysis applied to data for old adults only.

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

FIGURES


(50 ms)
500 ms
Warning Tone
1000 ms
Encoding
2500 or 5000 ms
Maintenance
until response or 3000 ms
Retrieval
800 ms
Intertrial Interval


F3
P2
Fz
F4
C3
Cz
N2
C4
P3
P300
Pz
P4
PO7
N1
Voltage (μV)
6
4
2
0
-2
0
200
400
600
800
Time (ms)
P1
Oz
PO8
Young High WM Load
Young Low WM Load
Old High WM Load
Old Low WM Load


r=0.512
p≤0.021
Old adults data
Young adults data
N2 Latency (in ms)
340
320
300
280
260
240
60
70
80
90
100
Accuracy (percentage of correct responses)

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

3.4 STUDY 4

Pinal, D., Zurrón, M. & Díaz, F. (submitted to Journal of Gerontology Series A Biological Sciences). An ERP Study of the Effects of Age, Load and Maintenance Duration on Working Memory Recognition.

Como xa se indicou no resumo do **Estudo 3**, tanto aquel como o presente **Estudo 4** foron deseñados para dar resposta o obxectivo IV deste traballo de doutoramento. Xa que logo, se o **Estudo 3** centrouse nos efectos da idade sobre os PE durante a codificación de información en memoria, o **Estudo 4** ten o seu foco nas diferenzas debidas ós procesos de avellentamento na actividade eléctrica cerebral durante a recuperación de información viso-espacial en MT, así como na interacción de ditos efectos da idade cos da carga en memoria e os da duración do período de mantemento.

De xeito similar ó indicado para o estudo anterior, o **Estudo 4** xurde ante a escaseza de estudos que analizasen o impacto da idade nos PE durante a recuperación/recoñecemento de información en MT, xa que a maior parte dos estudos previos sobre os efectos do avellentamento na recuperación de información realizáronse con paradigmas de memoria episódica a longo prazo. Ademais, tamén se empregou a manipulación da carga en memoria en busca de evidencias dunha menor capacidade da MT en adultos maiores que en mozos, posto que non se analizara previamente esta posibilidade para materiais visuais complexos (ver "Introduction" páx. 17). Mais aínda, o noso entender, non existen estudos previos que manipulasen a duración do período de mantemento a tal fin. Por último, quíxose examinar se, en liña cos resultados de estudos previos, existe unha diminución xeneralizada da velocidade do procesamento neural durante a recuperación, ou se coma no caso do **Estudo 3** esta diminución da velocidade só se reflicte en compoñentes específicos dos PE.

Para a consecución destes obxectivos analizáronse os mesmos datos condutuais que no **Estudo 3**, só que neste caso fíxose a través das puntuacións de eficiencia inversa (ver apartado 3.1 para máis detalles sobre estas puntuacións) e, ademais, realizáronse comparacións entre ambas condicións de duración do período de mantemento. Estas análises confirmaron os resultados referidos no **Estudo 3** e non revelaron efectos significativos da duración do período de mantemento sobre a execución na tarefa ED.

A nivel electrofisiolóxico, empregáronse os valores de latencia a pico e amplitude de liña base a pico dos compoñentes dos PE durante o recoñecemento de información na tarefa de ED correspondentes á mostra de 20 mozos e 20 adultos maiores sans. Ditos parámetros comparáronse entre grupos, condicións de carga en memoria e condicións de duración do período de mantemento, poñéndose especial interese nos efectos da idade e nas interaccións entre a idade e as outras dúas variables.

Os resultados das probas estatísticas non amosaron diferenzas entre grupos na latencia ou amplitude de P1 e N1. Non obstante, os resultados revelaron maiores latencias para N2 e P300 en adultos maiores que en mozos, aínda que non había diferenzas entre os dous grupos na amplitude dos compoñentes dos PE. Deste xeito, os resultados parecen indicar, como ocorreu no caso da codificación, que o procesamento perceptivo, reflectido nos compoñentes P1 e N1, tamén está preservado no cerebro humano avellentado durante a recuperación/recoñecemento de información en memoria. Así mesmo, a evidencia apunta que a diminución da velocidade de procesamento centrase na avaliación e categorización dos estímulos, as cales téñense asociado a N2 e P300, respectivamente. Polo que, estes resultados apoian os do **Estudo 3**, indicando que a diminución da velocidade de procesamento coa idade non é xeneralizada.

En canto as interacción entre os efectos da idade e os da duración do período de mantemento, unha duración longa do período de mantemento asociouse a unha maior amplitude de N1 que unha duración curta, só nos mozos. O que indica que os mozos no presente estudo modularon o procesamento perceptivo en función da duración do período de mantemento, en tanto que os adultos maiores non mostraron tal diferenza.

Polo que se refire ás interaccións da idade coa carga en memoria, a distribución de P300 no coiro cabeludo foi máis homoxénea en adultos maiores que en mozos. Isto debese a que nos maiores non se apreciaba o clásico pico máximo da amplitude de P300 en localizacións centro-parietais, o cal si se observou en mozos durante a condición de baixa carga en memoria. Polo tanto, os datos parecen apuntar que os adultos maiores teñen unha maior dependencia dos recursos frontais en relación cos parietais da que teñen os adultos novos. Este último achado, asemellase ó suxerido pola hipótese dun desprazamento do recrutamento de recursos de áreas posteriores a áreas anteriores coa idade (PASA, polas súas siglas en inglés). Esta hipótese xerouse na investigación dos procesos de recoñecemento na memoria episódica a longo prazo; xa que logo, os resultados do presente estudo parecen estender os postulados desta hipótese ós mecanismos de recoñecemento de información na MT viso-espacial.

Por último, é salientable que tanto a carga en memoria como a duración do período de mantemento tiveron efectos sobre a actividade eléctrica cerebral. Así, duracións longas do período de mantemento asociáronse a menores amplitudes de P1 e a onda lenta negativa, pero maiores amplitudes de P2 que duracións curtas. Tamén a latencia de N2 foi maior ante duracións longas do período de mantemento que ante duracións curtas. Pola súa parte, unha carga en memoria alta relacionouse con menores amplitudes de N1 e a onda lenta negativa. Non obstante, estes efectos foron independentes da idade dos participantes; o cal contrasta coa hipotética redución da capacidade da MT asociada á idade.

Deste xeito, o conxunto de resultados do presente traballo apuntan cara a existencia dunha diminución da velocidade de procesamento asociada á idade, a cal sería específica para os procesos de avaliación e clasificación do estímulo e non xeneralizada. Amais, os

efectos da carga en memoria e a duración do período de mantemento sobre a amplitude e latencia dos compoñentes dos PE son independentes da idade Non obstante, os adultos maiores presentaron unha maior dependencia dos recursos frontais en relación cos parietais que os mozos. Así, namentres os mozos só mostran unha distribución homoxénea da amplitude de P300 no pericranio cando a demanda cognitiva é alta, os adultos maiores presentan esta distribución xa en condicións de baixa carga en memoria. Este feito, xunto cos datos condutuais, parecen indicar que os adultos maiores teñen unha maior sensibilidade á carga en memoria que os mozos.

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

TITLE

An ERP Study of the Effects of Age, Load and Maintenance Duration Effects on Working Memory Recognition.

AUTHORS

Diego Pinal[1*], Montserrat Zurrón[1] and Fernando Díaz[1]

1 Applied Cognitive Neuroscience Laboratory, Department of Clinical Psychology and Psychobiology, Faculty of Psychology, Universidade de Santiago de Compostela, Galiza, Spain.

***Correspondence**:
Mr. Diego Pinal
Department of Clinical Psychology and Psychobiology,
Facultade de Psicoloxía, Campus Sur.
15782Santiago de Compostela, Spain
diego.pinal@usc.es
Tel: +34 881 881 396

RUNNING TITLE

Working memory recognition in aging.

ABSTRACT

Age-related decline in cognitive capacities has been attributed to a generalized slowing of processing speed and a reduction in working memory (WM) capacity. Nevertheless, it is unclear how age affects visuospatial WM recognition and its underlying brain electrical activity. Whether age modulates the effects of memory load or information maintenance duration, which determine the limits of WM, remains also elusive. Here, performance in a delayed match to sample task declined with age, particularly in conditions with high memory load. Event related potentials analysis revealed longer N2 and P300 latencies in old than young adults during WM recognition, which reflects slowing of stimulus evaluation and classification processes, respectively. Although there were no between groups differences in N2 or P300 amplitudes; the latter was more homogeneously distributed in old than young adults, which may indicate an age-related increased reliance in frontal vs parietal resources. Memory load and maintenance duration effects on brain activity were similar in both age groups. These behavioral and ERP results support an age-related decline in WM recognition, with slowing of processing speed limited to stimulus evaluation and categorization processes -with no effects on perceptual processes- and a posterior to anterior shift in the recruitment of neural resources.

KEYWORDS

Cognitive decline, electroencephalography, brain aging, slowing of processing, posterior-anterior shift

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

INTRODUCTION

As humans age, there is a certain generalized decline in cognitive capacities (1), which has been related (among other mechanisms) to a generalized slowing of processing speed (2) and to a decrease in processing resources (3). Recognition processes, defined as the identification of items (people, objects, words, etc.) as having been previously encountered or experienced, forms part of different memory systems. These processes are assumed to be among those abilities affected by age-related decline in cognitive performance (4,5). However, most research has focused on how aging affects long-term episodic memory recognition, while little is known about such effects on working memory (WM) recognition.

WM is a capacity-limited system that comprises the ability to mentally manipulate and hold in mind for brief periods of time (i.e. a few seconds) small amounts of information that are no longer available in the environment (6,7), thereby supporting complex cognition and many daily life activities (8). Some authors have suggested that the limits of WM capacity may also be reduced in old adults relative to young adults (9,10). These limits seem to be determined by the amount and complexity of information to be encoded into memory, the so-called memory load (11,12), and by the amount of time it has to be held in mind (13).

Delayed match to sample (DMS) and Sternberg tasks enable WM encoding, maintenance and recognition processes to be studied independently. These tasks involve a first stage in which participants are presented with information items to be encoded in memory and, after a variable brief time delay, a second stage in which a recognition judgment (e.g. equal/different, identification among alternatives) must be made on the basis of the previously memorized information. These types of task also enable experimental manipulation of memory load and the time that information has to be held in mind, by varying the amount or complexity of the items to be encoded in memory and the duration of the time delay between both task stages (maintenance period), respectively. Moreover, use of the event-related potentials (ERPs) technique enables study of the brain electrical activity in response to a defined event (e.g. presentation of a stimulus), with a temporal precision of milliseconds. The combined use of the above mentioned tasks and the ERP technique may represent an optimal means of testing for age-related differences in the brain electrical activity underlying WM recognition processes, and can also be used to establish whether memory load and maintenance period duration modulate any such differences.

Research undertaken using these tasks in combination with the ERP technique has shown that healthy aging modulates electrical brain activity during WM recognition. For instance, larger P1 amplitudes (14) and longer N1 latencies (14,15) have been observed in old adults than in young adults. Longer latencies and lower P300 amplitudes have also been observed (14,16,17); arguably, this pattern of results is generally consistent with

predictions from the aforementioned theories of an age-related generalized slowing of processing speed and of an age-related reduction in the capacity to allocate processing resources. Nevertheless, the effects of healthy aging on the latency and amplitude of P2 and N2 components remains controversial, since mixed results have been obtained during WM recognition in previous studies of DMS tasks (15,16). Therefore, further work is needed to determine the effects of aging on these ERP components.

Old adults are assumed to be more sensitive than young adults to the effects of memory load because of their reduced WM capacity (9,10). Indeed, it has been suggested, on the basis of findings from neuroimaging studies that old adults show similar memory load related modulations in brain activity as young adults, but when facing lower levels of memory load (18,19). Use of the ERP technique has revealed lower N1 (20,21) and P300 (20–22) amplitudes for high relative to low memory load conditions in healthy young participants during WM recognition in DMS tasks. Similar results have also been observed with older adults; however, no significant interaction between WM load and age-related effects on brain electrical activity was observed during WM recognition (14,17). The latter studies used visual presentation of 1, 3 or 5 digits, and therefore it is still unclear whether the hypothesized higher sensitivity of older adults to memory load would be observed in ERP components if other materials and means of manipulating WM load were used.

The amount of time that information has to be actively maintained in WM has been shown to modulate brain activity during the recognition stage of DMS tasks, since larger N2 amplitudes after long than short periods of information maintenance have been observed in healthy young adults (22,23). However, to the best of our knowledge, no previous ERP studies have assessed the effects of the duration of maintenance period in old adults at the recognition stage of a DMS task. In this regard, the existence of age-related differences in brain electrical activity during WM recognition due to the hypothesized reduced WM capacity of older adults is conceivable. Recent neuroimaging studies have identified a deficit in the maintenance of task relevant information and goals in old relative to young adults, which was accompanied by changes in brain activity during probe recognition in a continuous performance task (24).

The present study aimed to assess the effects of aging on brain electrical activity during the recognition stage of a DMS task, in which participants are required to encode and maintain in WM the pattern shown on a domino tile and to try to recognize the pattern from among three different alternatives shown a few seconds later. A second goal is to test possible interactions between aging effects and memory load and/or maintenance duration, as it has been suggested that the WM capacity is lower in old than in young adults. Both latter aspects were experimentally manipulated by changing the number of dots and their spatial configuration on the domino tiles and by varying the length of the maintenance period, respectively.

METHODS AND MATERIALS

Sample

The sample comprised 40 volunteers. All except three were right handed, as assessed by the Edinburgh Handedness Inventory (25). All participants had normal or corrected-to-normal vision and reported no history of neurological or psychiatric disorders. None of the participants were taking psychotropic medication and they were instructed to abstain from consuming alcohol and caffeine the day prior to the experimental session. All participants gave their informed consent before the experimental session, and the study protocol was approved by the ethical committee of the University of Santiago de Compostela (USC).

Participants were further divided in two groups (each with 16 females): 20 young adults (mean age = 23.85 ± 3.18 years) were recruited from the USC alumni, and 20 healthy old adults (mean age = 67.80 ± 7.69 years) were recruited from USC courses for older adults and from two different cultural associations where they participate in cognitively demanding activities (foreign language learning, informatics courses, etc.). The two groups differed significantly in time spent in formal education (young: 16.25 ± 1.25 years, elderly: 14.12 ± 3.93 years; $t(18.79) = -2.160$, $p \leq .044$) but obtained equivalent scores in the Spanish version of the Wechsler Adults Intelligence Scale vocabulary subtest (26) (young: 47.95 ± 5.22, old: 48.15 ± 8.68; $t(31.41) = 0.89$, $p \leq .930$).

Experimental protocol

Participants performed the visual DMS task illustrated in Figure 1A, which is described in detail elsewhere (22). The task comprised 200 trials divided into two blocks with a 5 minute inter-block interval. Participants also received a short training on the task before EEG registration. Each trial began with a warning tone (1000 Hz pitch, 50 ms duration) indicating the start of a 500 ms prestimulus interval. A domino tile (sample stimulus), was then presented (encoding stage) and remained in the screen for 1000 ms. A blank screen delay of 2500 or 5000 ms (50% of probability of appearance) (maintenance period), was followed by presentation of three new dominoes (probe stimuli) (recognition stage). The probe stimuli were presented until the participant's response or a maximum of 3000 ms, and the inter-trial interval was 800 ms. To minimize ocular artifacts, a fixation cross was placed in the center of the screen during the periods in which no stimulation was presented. Presentation of stimuli and recording of responses were controlled by Presentation® software (Neurobehavioral Systems, Inc., Albany, CA, USA).

In the present study analyses were restricted to the probe stimulus presentation, during which participants are required to retrieve sample stimulus information, compare it with the new visual input and identify the previously presented domino tile. Each domino tile (8 cm high x 4 cm wide) consisted of two equally sized, vertically arranged white squares and included two to five black dots (1 cm diameter) located at the corners of each square,

leaving a 1 cm gap between them and a 0.5 cm gap from the square boundaries. Each sample stimulus was presented on a black background in the center of a 19" monitor (refresh rate: 100 Hz) located at a distance of 1 m from the participant's eyes, so that it subtended a visual angle of 4.58° x 2.28°. As regards probe stimuli, the dominoes were presented simultaneously in the horizontal midline of the monitor (4 cm apart from each other). Only one was identical to the sample stimulus (target), and participants were asked to identify this as quickly and accurately as possible by pressing the button corresponding to its position on screen (left, center or right) from three response buttons arranged horizontally on a response device (Cedrus ®, model RB-530). The response button was counterbalanced across trials so that no more than three consecutive trials involved pressing the same button.

Memory load was manipulated between trials by changing the number of dots on the dominoes (Fig. 1B). The dominoes were grouped into two memory load conditions: a low load condition (LL) comprising dominoes with two or three dots, and a high load condition (HL) comprising dominoes with four or five dots. All dominoes in a trial pertain to the same memory load condition. The first task block consisted of 90 low memory load trials, while the second block consisted of 110 high memory load trials. The percentage of repeated dominoes was maintained constant in both blocks (20%). The HL block included more trials than the LL block to ensure a good signal-to-noise ratio, since a higher proportion of errors was expected for that block.

The duration of the maintenance period was also manipulated. Two conditions were generated: a short maintenance period (SMP) including trials with a 2.5 s delay between sample and probe stimuli, and a long maintenance period (LMP) comprising trials with a 5 s delay between the stimuli. Duration of the maintenance period was pseudo-randomly distributed across trials so that half of the trials in each block pertain to each condition of the maintenance period duration, while avoiding more than five consecutive trials with the same maintenance period duration.

EEG recordings and signal processing

During the experimental session, participants sat in a comfortable armchair inside a noise and light attenuated Faraday chamber. The EEG activity was recorded through 51 active electrodes inserted in a cap and placed in the standard positions of the 10-10 system, with fronto-polar ground and nose tip reference. All electrode impedances were maintained below 8 kΩ. EOG activity was monitored by placing two electrodes in the outer canthi of both eyes (HEOG) and another two electrodes above and below the right eye (VEOG). The EEG signal was analogically filtered between 0.01 to 100 Hz, sampled at 500 Hz and digitally recorded for off-line analyses.

The recorded data were passed through a digital phase-shift free Butterworth filter with the high cut-off frequency at half power (-3 dB) set at 30 Hz (12 dB/octave roll-off)

and with a low cut-off frequency at half power set at 0.1 Hz (12 dB/octave roll-off). A notch-filter centered at 50 Hz was also applied to avoid contamination of electrical line noise. Ocular and muscular artifacts were corrected using the Infomax algorithm in an Independent Component Analysis as implemented in Brain Vision Analyzer (v.2 Brain Products GmbH). Semi-automatic artifact rejection was also conducted (i.e. trials with voltage changes of ±125 μV were excluded). Data were segmented in epochs ranging from 200 ms prior to probe stimuli presentation to 1000 ms post-stimuli, and they were baseline corrected with the mean activity in the 200 ms prior to the probe stimuli onset. Only epochs corresponding to correctly answered trials were included in further analyses.

Behavioral and electrophysiological data

The proportion of correct responses and reaction times (RTs) for the correctly responded trials were registered for each participant and experimental condition (LL-SMP, LL-LMP, HL-SMP and HL-LMP). Both measures were combined in the Inverse Efficiency (IE) score, which is calculated as the mean RT divided by the proportion of correct responses (27). A increase in RT or decrease in the proportion of correct responses would thus result in an increase in the IE score; hence, higher IE scores reflect poorer performance than lower scores. IE can be considered as a "corrected reaction time" and its use avoids possible contamination of speed-accuracy tradeoffs or response criterion shifts (28). The IE was calculated for each subject and each condition.

As regards electrophysiological data, separate averaged ERP waves to probe stimuli were obtained for each experimental condition (LL-SMP, LL-LMP, HL-SMP and HL-LMP). On the basis of the reports reviewed in the introduction section as well as visual inspection of the ERP waveform, the components of interest for the present study were: P1, N1, P2, N2, P300; and a Negative Slow Wave (NSW). Peak latency and baseline to peak amplitude of these ERP components were measured as follows: P1 was considered the maximum peak at O1, Oz and O2 between 85 and 145 ms post-stimuli; N1 was defined as the most negative peak between 150 and 210 ms after stimuli presentation at P9, P7, P8 and P10; P2 was measured as the largest positive peak at F3, Fz and F4 between 180 and 250 ms post-stimuli; N2 was considered the maximum negative peak at F3, Fz, F4, C3, Cz and C4 between 230 and 300 ms after probe stimuli onset and always as the negativity preceding the P300 component; P300 was identified as the maximum positive peak separately at P3, Pz and P4, and at F3, Fz and F4, between 300 and 500 ms post-stimuli. For each component, latency and amplitude data were averaged across the selected electrodes, so that the mean values for each component were included in the statistical analyses. As regards the NSW, the mean amplitudes between 700 and 850 ms post-stimuli and from 851 to 1000 ms post-stimuli were measured at Fz, Cz, Pz and Oz electrodes.

Table 1 includes the mean values and standard deviation of these ERP parameters for each group in each experimental condition.

Statistical analyses

Age-related effects on behavioral performance, as reflected in the IE scores for the visual DMS task, and also those of memory load and duration of the maintenance period were assessed by a mixed design analysis of variance (ANOVA), with the between subjects factor Age Group (young and elderly) and the within-subject factors Memory Load (LL and HL) and Maintenance Duration (SMP and LMP).

In order to assess age-related effects on the ERP parameters as well as the potential effects of memory load and duration of the maintenance period, mixed design ANOVAs were applied to the mean latency and amplitude of the ERP components P1, N1, P2, N2, with the between subjects factor Age Group (young and elderly) and the within subjects factors Memory Load (LL and HL) and Maintenance Duration (SMP and LMP). Two mixed design ANOVAs with the same factors were applied to the mean amplitude values of the NSW between 700 and 850 ms post-stimulus and from 851 to 1000 ms after stimulus onset.

For P300, which was measured at frontal and parietal sites, mixed design ANOVAs were applied to the amplitude and latency values, with the between subjects factor Age Group (young and elderly) and the within subjects factors Memory Load (LL and HL), Maintenance Duration (SMP and LMP) and Region (frontal and parietal).

In all the mixed ANOVAs performed in the present study statistical significance was set at $p \leq .05$. Greenhouse-Geisser correction was applied whenever the sphericity assumption was violated, while Bonferroni adjustment was used to control for multiple comparisons.

RESULTS

Behavioral performance

ANOVA of the IE scores revealed a significant main effect of the Age Group factor [$F(1,38)=65.43$, $p<0.001$], as well as a significant main effect of the Memory Load factor [$F(1,38)=91.76$, $p<0.001$].

The interaction between both factors was also statistically significant [$F(1,38)=19.73$, $p<0.001$]. Thus, IE scores were longer (note that they are expressed in ms) for old than young adults in both memory load conditions ($p \leq 0.001$), while high load conditions yielded significantly longer IE scores than low load conditions in both age groups ($p \leq 0.001$) (Table 2). To further explore this interaction, IE scores for the low load condition were subtracted from those of the high memory load for each participant. A t-test was used to compare each group. Significantly longer values were observed in the old than the young group [$t(27.05)=4.44$, $p<0.001$], indicating greater increases of IE scores with memory load in the older than the young group (Fig. 2).

No significant main effect or interaction was observed for the factor Maintenance Duration.

Electrical brain activity

ERP Latencies

As regards latencies of the ERP components, ANOVAs revealed significant main effects for the factor Age Group on N2 and P300 [$F(1,38)=25.52$, $p<0.001$ and $F(1,38)=24.16$, $p<0.001$, respectively]. In both cases, latencies were significantly longer in old than young adults.

No significant main effects of Memory Load were observed. However, a significant interaction between the factors Memory Load and Region was observed for P300 [$F(1,38)=6.04$, $p\leq0.019$]; latencies were significantly longer in HL than in LL conditions at frontal electrodes ($p\leq.039$) (Fig. 3).

Significant main effects involving factor Maintenance Duration were observed for N2 [$F(1,38)=4.53$, $p\leq0.040$]. N2 latencies were significantly longer in LMP than in SMP conditions (Fig. 4).

ERP Amplitudes

No main effects involving factor Age Group were found to be statistically significant in the ANOVAs applied to the amplitudes of ERP components. Nevertheless, a significant interaction between Age Group and Maintenance Duration was found for N1 amplitude [$F(1,38)=11.07$, $p\leq0.002$], with significantly larger amplitudes in LMP than in SMP trials only for the young adults ($p\leq0.001$). A significant interaction between Age Group, Memory Load and Region was observed for P300 [$F(1,38)=7.08$, $p\leq0.011$]. Thus, in low load trials, the P300 amplitude was larger in parietal than in frontal regions only in the young adults ($p\leq.021$) (Fig. 3).

Significant main effects of factor Memory Load were found for N1 amplitude and for the NSW mean amplitude in the time window between 700 and 850 ms post-stimuli [$F(1,38)=6.79$, $p\leq0.013$ and $F(1,38)=5.14$, $p\leq0.029$, respectively]. In both effects, the amplitudes were significantly lower in HL than in LL trials (Fig. 3).

Memory Load also showed a significant interaction with Maintenance Duration for N2 amplitude [$F(1,38)=6.50$, $p\leq0.015$, respectively]. Therefore, the N2 amplitude was significantly lower in HL than in LL conditions only in trials with short durations of maintenance period ($p<0.001$).

As regards the Maintenance Duration factor, significant main effects were observed for P1 [$F(1,38)=5.64$, $p\leq0.023$] and P2 amplitudes [$F(1,38)=6.01$, $p\leq0.019$], as well as NSW mean amplitude in the time window between 700 and 850 ms post-stimuli [$F(1,38)=4.12$, $p\leq0.049$]. While the amplitudes of P1 and the NSW were significantly

lower in LMP than SMP conditions (Fig 4), the P2 amplitude was significantly larger in LMP than SMP conditions (Fig 4).

DISCUSSION

Task performance

Performance of the DMS task was poorer in old than in young adults. This is consistent with previous findings indicating an age-related WM decline in the execution of different cognitive tasks (1). In addition, high memory load also yielded a decrease in task performance; this confirms previous findings of a detrimental effect of memory load on task performance (11,12,22).

Interestingly, the detrimental effect of memory load was more marked in old than in young adults. This effect was not observed in previous studies with DMS tasks that used visually presented digits (14,17). Use of this type of stimuli may have created a simpler condition than in the present study, as judged from the RTs and accuracy rates. This may have precluded observation of the proposed higher sensitivity to memory load in old adults. Indeed, the significant interaction between memory load and age effects is consistent with the findings of a previous study with a DMS task that used abstract shapes as stimuli (29). Consequently, it seems that at a behavioral level, older adults are more sensitive to memory load than young adults when performing tasks with complex visual stimuli.

Maintenance duration, on the other hand, had no effect on task performance, which contrasts with previous findings (29) of significant effects of maintenance duration on the execution of young and old adults in a DMS task with shorter retention intervals (i.e. 500 and 2500 ms) than those used in the present study. This difference may explain the contradictory findings. Therefore, it seems that at the behavioral level, old and young adults are not affected by the duration of the maintenance period in the present visuospatial DMS task.

Electrical brain activity during WM recognition

ERP latencies

Age-related differences in brain electrical activity timing began at around 250 ms after presentation of probe stimuli and were reflected as longer N2 and P300 latencies in old than in young adults.

In contrast with the age-related modulation of N1 latency during WM recognition reported in previous studies (14,15), no differences in N1 latency between age groups were observed in the present study. This component has been associated with perceptual processing of complex visual inputs (30,31), and therefore inter-study differences in the type of stimuli and familiarity with these may be a key factor explaining the discrepancy in

the results. Nevertheless, the present findings may indicate preserved perceptual processing speed during WM recognition in healthy aging.

The N2 component has been related to initial evaluation of the stimulus (32), which includes evaluation of the probe stimuli and comparison of each domino with the memory template of the sample stimulus during WM recognition (33). Similarly, P300 latency is considered an indicator of the amount of time required for completion of stimulus evaluation and classification processes (34,35). Although some studies did not find age-related differences in N2 latency (16,17), longer P300 latencies are a common and consistent finding in oddball tasks or during WM encoding in DMS tasks (4,14,16,17). Thus, the present results extend previous findings as they reveal that age-related slowing of processing speed during WM recognition affects probe stimuli evaluation and classification processes.

Additionally, memory load affected P300 latency. Longer P300 latencies in high than low memory load trials were found, which is consistent with previous findings in P300 research (35,36). Hence, the present finding may indicate that, during WM recognition, evaluation and classification of the probe stimuli -based on the memory template of the sample stimulus- takes longer in the high than in the low memory load condition, independently of age.

With regard to maintenance duration effects, longer N2 latencies were found in trials with long than short durations, in both age groups. Thus, after long maintenance periods, initial evaluation of probe stimuli and comparison with the memory template of the sample stimulus is probably delayed relative to short maintenance periods. It is possible that this effect is related to the enfeeblement of the memory traces due to the mere passage of time during the maintenance period, as suggested from time-based decay theories (37).

ERP amplitudes

Although there were no main effects of age group, age-related effects interacted with those of maintenance duration on N1 and those of memory load on P300.

The N1 amplitudes were only larger after long that after short maintenance periods in the young participants. Lower N1 amplitude during WM recognition under high than low cognitive demands has been interpreted as a sign of a reduction in the amount of processing resources allocated to perceptual processing, probably due to a greater distribution of these resources between perceptual processing of new visual inputs and maintenance of previously seen visual stimuli (20). Accordingly, in the present study it seems that young participants were able to allocate more processing resources to perceptual processing after long than after short maintenance periods, as the distribution of processing resources between maintenance and perceptual processes is lower in the former than the in latter condition. Interestingly, no such differences were observed in old adults.

The P300 amplitude was larger at parietal than at frontal sites in the young subjects during the low load condition, while no inter-electrode differences were observed in the older group. A topographic distribution with parietal maximum has been consistently reported in P300 research in healthy young adults (35), as well as a more homogeneous topographic distribution of this component amplitude in healthy old adults (38–40). Such homogeneous distribution due to the loss of a clear parietal maximum for P300 amplitude has been considered an indicator of maintained or increased frontal activity with aging. Such changes are consistent with the proposed posterior to anterior shift with aging (PASA) hypothesis, which was originally supported by data from episodic memory retrieval and visual perceptual tasks (41). This hypothesis postulates that recruitment of anterior or frontal resources occurs with aging to compensate for a decrease in posterior (more specific) processing resources. Thus, the present findings extend the PASA hypothesis to WM recognition processes.

Furthermore, independently of the age of participants, memory load affects the amplitude of N1, the mean amplitude of the first period of the NSW, and N2 amplitude only in SMP trials. The amplitudes were smaller in high than low memory load trials in all three cases. In the DMS task, recognition of the domino tiles in the high load condition probably requires the distribution of processing resources to more mental operations as well as greater effort than in the low load condition. This effort involves processing the spatial configuration of the dots on the domino, evaluating and comparing the three items of the probe stimuli against the memory trace of the sample stimulus and carrying out post-categorization and response preparation processes. This may yield a reduction in N1, N2 and NSW amplitudes, as these components presumably reflect each of these respective processes (21,22,32,33).

The maintenance period duration modulated P1 and P2 amplitudes, and also the first interval of the NSW mean amplitude in both age groups. The amplitudes of P1 and NSW were smaller after long than after short maintenance periods, while the amplitude of P2 was larger. Although it is difficult to interpret the effects on brain electrical activity found for maintenance duration in the present study, it is clear that maintenance duration modulates cognitive demands, as previously suggested (13). The effects of maintenance duration were independent of the age of participants. Therefore, considered together with behavioral results, the present pattern of results may indicate that old and young adults are similarly affected by maintenance duration at both behavioral and electrophysiological levels. This contrasts with the suggested age-related reduction in WM capacity. Accordingly, future work is warranted to further our understanding of the impact of maintenance duration on the brain activity underlying WM recognition processes.

CONCLUSION

In summary, the behavioral data indicate an age-related decline in performance related to visuospatial WM recognition, as well as a greater sensitivity to WM load in old adults.

The electrophysiological data showed a specific age-related slowing in the evaluation and classification of the probe stimulus, but not in perceptual processes. The data also indicated a more homogeneous scalp distribution of P300 in old than in young adults, which supports an age-related posterior to anterior shift in the recruitment of neural resources during WM recognition. Furthermore, the effects of maintenance duration effects were mainly independent of age for both behavioral and electrophysiological data.

FUNDING

This work was financially supported by the Spanish Government's Ministerios de Educación (BES 2008-005929) and Economía y Competitividad (PSI2010-22224-C03-03); and by the Galician Government's Consellería de Economía e Industria (10 PXIB 211070 PR), and Consellería de Educación e Ordenación Universitaria (Axudas para a consolidación e estruturación de unidades de investigación competitivas do sistema universitario de Galicia. Ref: GPC 2014/047).

CONFLICT OF INTEREST STATEMENT

None to declare.

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

REFERENCES

1. Park DC, Lautenschlager G, Hedden T, Davidson NS, Smith AD, Smith PK. Models of visuospatial and verbal memory across the adult life span. Psychol Aging. 2002;17(2):299–320.
2. Salthouse TA. The processing-speed theory of adult age differences in cognition. Psychol Rev. 1996 Jul;103(3):403–28.
3. Craik FIM, Byrd M. Aging and cognitive deficits: The role of attentional resources. In: Craik FIM, Trehub S, editors. Aging and Cognitive Processes: advances in the study of communication and affect. New York: Plenum Press; 1982. p. 191–211.
4. Friedman D. The components of aging. In: Luck SJ, Kappenman ES, editors. Oxford Handbook of event-related potential components. 2012th ed. New York: Oxford University Press; 2012. p. 513–36.
5. Friedman D. The cognitive aging of episodic memory: a view based on the event-related brain potential. Front Behav Neurosci. 2013 Jan;7(111).
6. Baddeley A, Hitch G. Working Memory. Psychol Learn Motiv. American Association for the Advancement of Science; 1974;8:47–89.
7. Baddeley A. Working Memory: Theories, Models, and Controversies. Annu Rev Psychol. 2012 Dec 8;63(12):12.1–12.29.
8. Shah P, Miyake A. Models of working memory. An Introduction. In: Miyake A, Shah P, editors. Models of working memory: Mechanisms of active maintenance and executive control. 1st ed. New York: Cambridge University Press; 1999. p. 1–27.
9. Salthouse TA. Working memory as a processing resource in cognitive aging. Dev Rev. 1990;10(1):101–24.
10. Park DC. The basic mechanism, accounting for age-related decline in cognitive function. In: Park DC, Schwarz N, editors. Cognitive aging: A primer. Philadelphia (PA): Psychology Press; 2000. p. 3–21.
11. Luck SJ, Vogel EK. The capacity of visual working memory for features and conjunctions. Nature. 1997 Nov 20;390(6657):279–81.

12. Alvarez GA, Cavanagh P. The capacity of visual short-term memory is set both by visual information load and by number of objects. Psychol Sci. 2004 Feb;15(2):106–11.

13. Barch DM, Braver TS, Nystrom LE, Forman SD, Noll DC, Cohen JD. Dissociating working memory from task difficulty in human prefrontal cortex. Neuropsychologia. 1997 Oct;35(10):1373–80.

14. Pelosi L, Blumhardt LD. Effects of age on working memory: an event-related potential study. Cogn Brain Res. 1999 Jan;7(3):321–34.

15. Müller NG, Knight RT. Age-related changes in fronto-parietal networks during spatial memory: an ERP study. Cogn Brain Res. 2002 Apr;13(2):221–34.

16. Knott V, Millar A, Dulude L, Bradford L, Alwahhabi F, Lau T, et al. Event-related potentials in young and elderly adults during a visual spatial working memory task. Clin EEG Neurosci. 2004;35(4):185–92.

17. Pratt H, Michalewski HJ, Patterson J V, Starr A. Brain potentials in a memory-scanning task. II. Effects of aging on potentials to the probes. Electroencephalogr Clin Neurophysiol. 1989 Jun;72(6):507–17.

18. Park DC, Reuter-Lorenz PA. The adaptive brain: aging and neurocognitive scaffolding. Annu Rev Psychol. 2009 Jan;60:21.1–21.24.

19. Cabeza R, Dennis NA. Frontal lobes and aging: Deterioration and Compensation. In: Stuss DT, Knight RT, editors. Principles of Frontal Lobe Function. 2nd ed. New York: Oxford University Press, USA; 2013. p. 628–52.

20. Morgan HM, Klein C, Boehm SG, Shapiro KL, Linden DEJ. Working memory load for faces modulates P300, N170, and N250r. J Cogn Neurosci. MIT Press; 2008;20(6):989–1002.

21. Soria Bauser DA, Mayer K, Daum I, Suchan B. Encoding/retrieval dissociation in working memory for human body forms. Behav Brain Res. Elsevier B.V.; 2011 Jun 20;220(1):65–73.

22. Pinal D, Zurrón M, Díaz F. Effects of load and maintenance duration on the time course of information encoding and retrieval in working memory: from perceptual

analysis to post-categorization processes. Front Hum Neurosci. Frontiers; 2014 Jan 1;8(165).

23. Van der Ham IJM, van Strien JW, Oleksiak A, van Wezel RJA, Postma A. Temporal characteristics of working memory for spatial relations: An ERP study. Int J Psychophysiol. Elsevier; 2010;77(2):83–94.
24. Paxton JL, Barch DM, Racine CA, Braver TS. Cognitive control, goal maintenance, and prefrontal function in healthy aging. Cereb cortex. 2008 May;18(5):1010–28.
25. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. Elsevier; 1971;9(1):97–113.
26. Wechsler D. Wechsler Adult Intelligence Scale—Third edition. 3rd ed. San Antonio, Texas.: The Psychological Corporation; 1997.
27. Townsend JT, Ashby FG. Methods of Modeling Capacity in Simple Processing Systems. In: Castellan NJ, Restle F, editors. Cognitive theory (Volume 3). Hillsdale, New Jersey: Lawrence Erlbaum Associates Ltd; 1978. p. 199–239.
28. Kennett S, Eimer M, Spence C, Driver J. Tactile-visual links in exogenous spatial attention under different postures: convergent evidence from psychophysics and ERPs. J Cogn Neurosci. 2001 May 15;13(4):1–16.
29. Chen J, Hale S, Myerson J. Effects of domain, retention interval, and information load on young and older adults' visuospatial working memory. Aging, Neuropsychol Cogn. 2003;10(2):122–33.
30. Vogel EK, Luck SJ. The visual N1 component as an index of a discrimination process. Psychophysiology. 2000 Mar;37(2):190–203.
31. Itier RJ, Taylor MJ. N170 or N1? Spatiotemporal Differences between Object and Face Processing Using ERPs. Cereb Cortex. 2004 Feb 1;14(2):132–42.
32. Folstein JR, van Petten C. Influence of cognitive control and mismatch on the N2 component of the ERP: a review. Psychophysiology. 2008 Jan;45(1):152–70.
33. Yin J, Gao Z, Jin X, Ye L, Shen M, Shui R. Tracking the mismatch information in visual short term memory: an event-related potential study. Neurosci Lett. Elsevier Ireland Ltd; 2011 Mar 10;491(1):26–30.

34. Kutas M, McCarthy G, Donchin E. Augmenting mental chronometry: The P300 as a measure of stimulus evaluation time. Science (80-). 1977;197(4305):792–5.

35. Polich J. Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol. 2007 Oct;118(10):2128–48.

36. Verleger R. On the utility of P3 latency as an index of mental chronometry. Psychophysiology. 1997;34:131–56.

37. Cornelissen FW, Greenlee MW. Visual memory for random block patterns defined by luminance and color contrast. Vision Res. 2000 Jan;40(3):287–99.

38. Amenedo E, Díaz F. Effects of aging on middle-latency auditory evoked potentials: a cross-sectional study. Biol Psychiatry. 1998 Mar 1;43(3):210–9.

39. Fjell AM, Walhovd KB. P300 and neuropsychological tests as measures of aging: scalp topography and cognitive changes. Brain Topogr. 2001 Jan;14(1):25–40.

40. O'Connell RG, Balsters JH, Kilcullen SM, Campbell W, Bokde AW, Lai R, et al. A simultaneous ERP/fMRI investigation of the P300 aging effect. Neurobiol Aging. Elsevier Inc.; 2012 Oct;33(10):2448–61.

41. Davis SW, Dennis NA, Daselaar SM, Fleck MS, Cabeza R. Que PASA? The posterior-anterior shift in aging. Cereb Cortex. 2008 May;18(5):1201–9.

TABLES

Table 1. *Parameters of ERP components*. Latency (Lat), in milliseconds, and amplitude (Amp), in μV, for each group and memory load condition. Mean value ± standard deviation.

		P1		N1		P2		N2		P3 FRONTAL		P3 PARIETAL		NSW 701-850 ms	NSW 851-1000 ms
		Lat	*Amp*	*Lat*	*Amp*	*Lat*	*Amp*	*Lat*	*Amp*	*Lat*	*Amp*	*Lat*	*Amp*	*Amp*	*Amp*
ELDERLY	**LL**	105.1	3.7	175.9	-4.3	201.9	3.0	292.1	-4.8	414.4	1.8	417.0	1.6	-2.6	-3.0
		± 15.9	± 3.7	± 15.8	± 2.9	± 12.9	±3.1	± 15.6	± 2.5	± 27.7	± 1.7	± 29.5	± 3.2	± 3.1	± 3.5
	HL	105.2	3.3	173.7	-3.8	203.9	2.9	296.2	-3.8	404.0	1.6	419.2	1.4	-2.0	-2.8
		± 14.2	± 2.8	± 13.2	± 2.5	± 15.4	± 3.3	± 15.6	± 2.5	± 40.3	± 1.7	± 30.3	± 3.0	± 2.8	± 2.6
	SMP	103.6	3.8	174.1	-4.4	201.5	2.3	288.5	-4.6	408.9	1.6	412.5	1.1	-2.9	-3.5
		± 15.3	± 3.5	± 14.1	± 2.6	± 13.4	± 3.7	± 20.2	± 3.3	± 39.7	± 2.2	± 38.0	± 3.2	± 3.7	± 3.9
	LMP	106.8	3.3	175.5	-3.8	204.2	3.6	299.8	-4.0	409.5	1.7	423.7	1.8	-1.8	-2.4
		± 16.9	± 3.3	± 15.7	±3.4	± 18.3	± 2.9	± 17.6	± 2.5	± 38.8	± 1.6	± 28.4	± 3.3	± 2.7	± 2.9
YOUNG	**LL**	104.9	4.5	172.4	-4.4	198.4	3.4	271.2	-4.5	366.6	1.1	374.0	3.5	-4.6	-5.5
		± 17.7	± 5.1	± 15.7	± 2.5	± 11.2	± 3.4	± 15.4	± 3.9	± 34.8	± 3.0	± 32.1	± 5.5	± 4.6	± 4.7
	HL	105.6	4.7	175.5	-3.7	199.1	4.0	269.8	-3.1	358.8	1.7	378.0	2.9	-4.1	-5.1
		± 16.8	± 4.2	± 13.3	± 2.6	± 13.9	± 2.8	± 17.6	± 4.2	± 36.1	± 3.1	± 37.9	± 5.6	± 5.0	± 5.0
	SMP	106.6	5.2	175.7	-3.0	197.5	3.5	269.3	-4.0	357.8	1.3	372.0	3.0	-4.9	-5.7
		± 17.9	± 4.8	± 13.2	± 2.4	± 11.4	± 3.5	± 17.2	± 4.3	± 34.4	± 3.4	± 37.2	± 5.8	± 5.3	± 5.0
	LMP	103.9	4.0	172.2	-5.1	200.0	3.9	271.6	-3.5	367.7	1.5	380.0	3.4	-3.8	-4.9
		± 16.6	± 4.7	± 15.4	± 2.9	± 14.3	± 2.9	± 16.6	± 4.2	± 43.7	± 2.9	± 44.4	± 5.5	± 4.8	± 5.3

Table 2. *Behavioral data.* Inverse Efficiency (IE) scores and reaction times (RT), expressed in ms, and accuracy rates (Acc), expressed as percentages, for each group in each memory load and maintenance duration condition. Mean value ± standard deviation.

	Elderly						**Young**					
	Low Load			High Load			Low Load			High Load		
	IE	RT	Acc	IE	RT	Acc	IE	RT	Acc	IE	RT	Acc
Short Maintenance Duration	1694.6 ± 307.5	1450.6 ± 192.9	86.6 ± 8.4	2169.4 ± 352.1	1689.8 ± 163.5	79.3 ± 11.0	1137.1 ± 229.2	1061.6 ± 193.0	93.7 ± 4.2	1324.1 ± 234.1	1230.7 ± 203.7	93.2 ± 3.5
Long Maintenance Duration	1727.4 ± 340.3	1530.1 ± 208.8	89.9 ± 8.9	2184.0 ± 491.7	1668.2 ± 175.6	78.8 ± 13.1	1117.7 ± 232.0	1079.8 ± 208.7	96.9 ± 3.2	1272.0 ± 257.6	1187.8 ± 220.3	93.7 ± 3.7

FIGURE LEGENDS

Fig. 1 Diagram of the delayed match to sample task used in the study. Inside a red square the recognition stage, which was the focus of the analyses carried out in the present work.

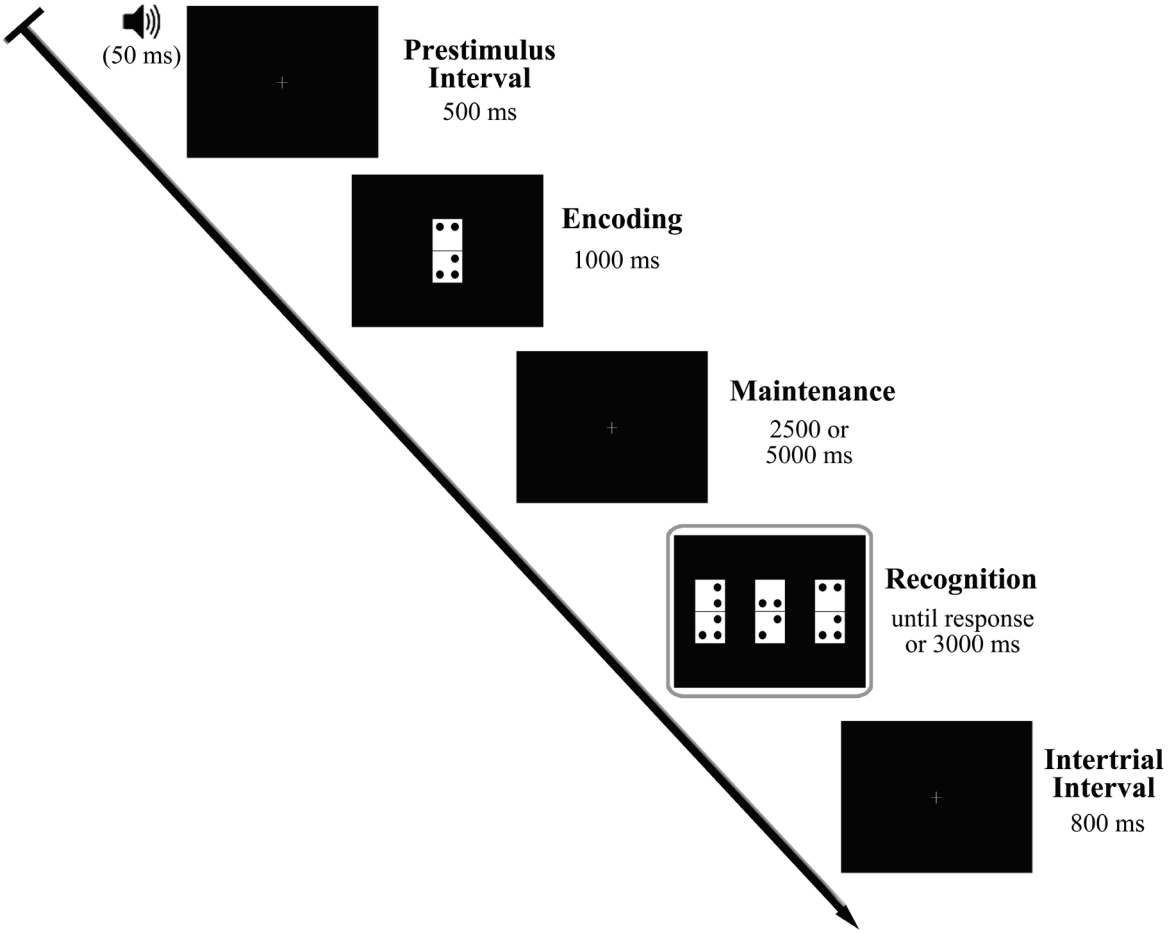
Fig 2. Increase in IE scores from low memory load to high memory load conditions for each group. Segments depicting the slope of the increase in IE scores from the low load memory condtion to the high load memory condition for each group.

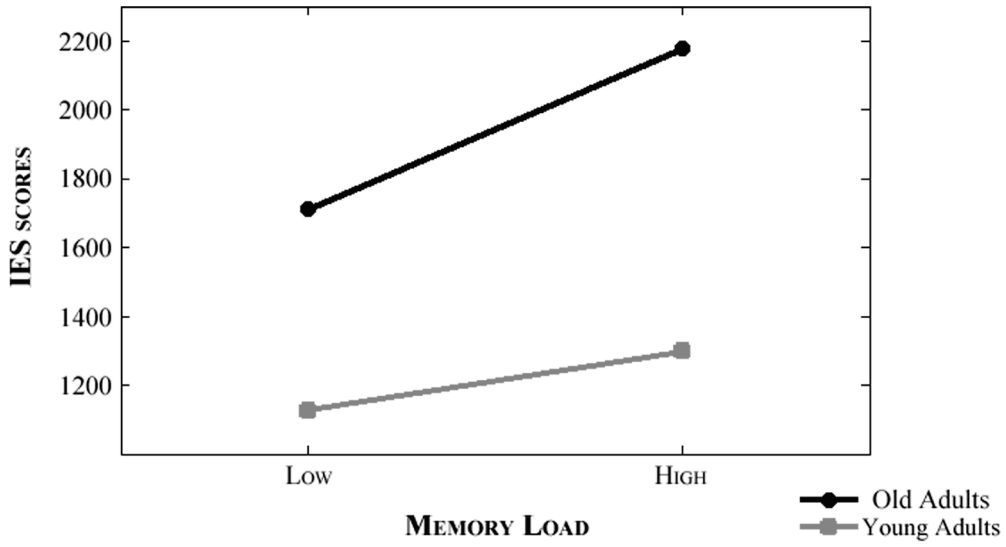
Fig 3. ERP waveforms at several electrode locations during recognition of information in WM. ERP waveforms for each group and memory load conditions.

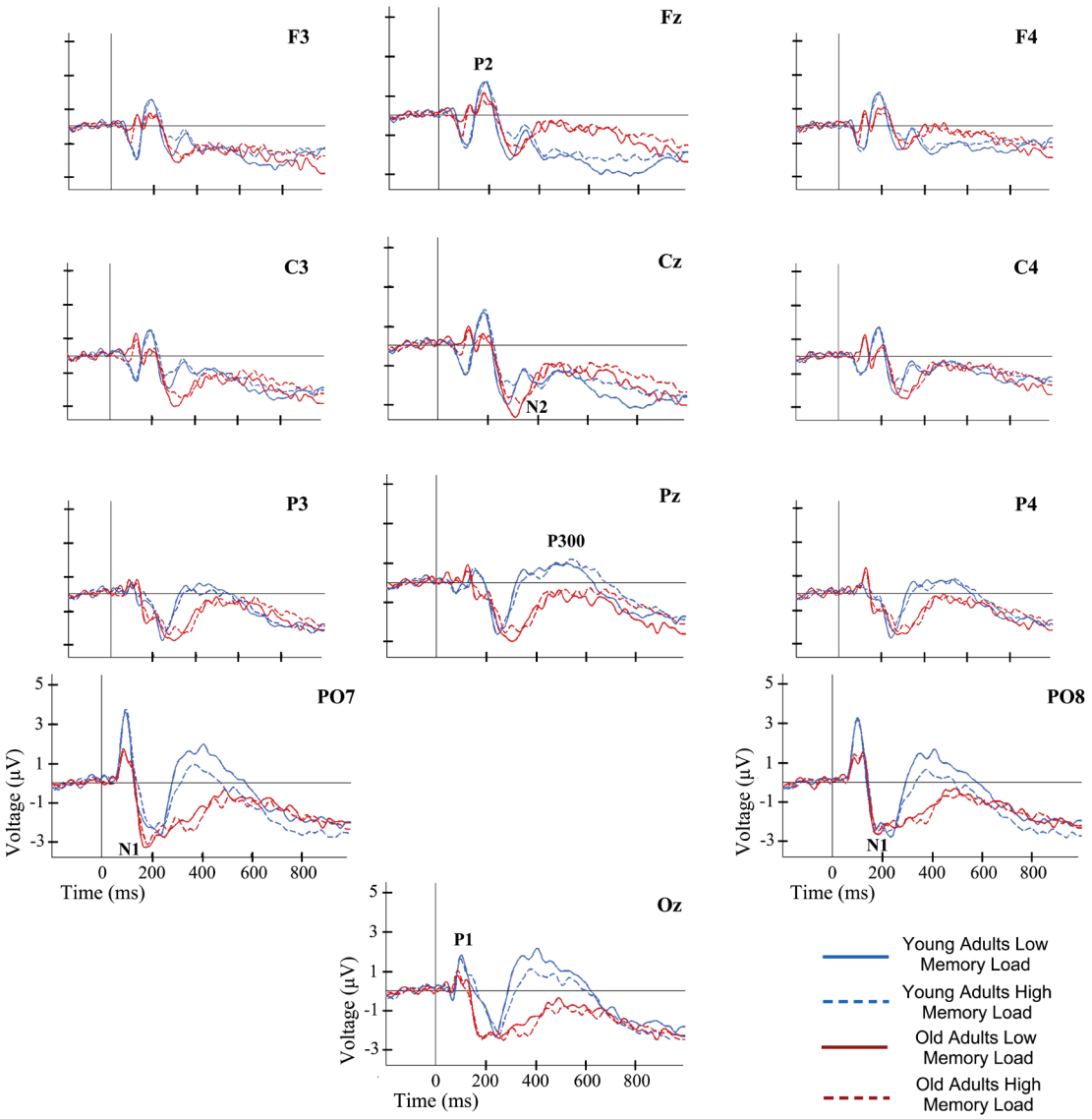
Fig 4. ERP waveforms at several electrode locations during recognition of information in WM. ERP waveforms for each group and maintenance duration conditions.

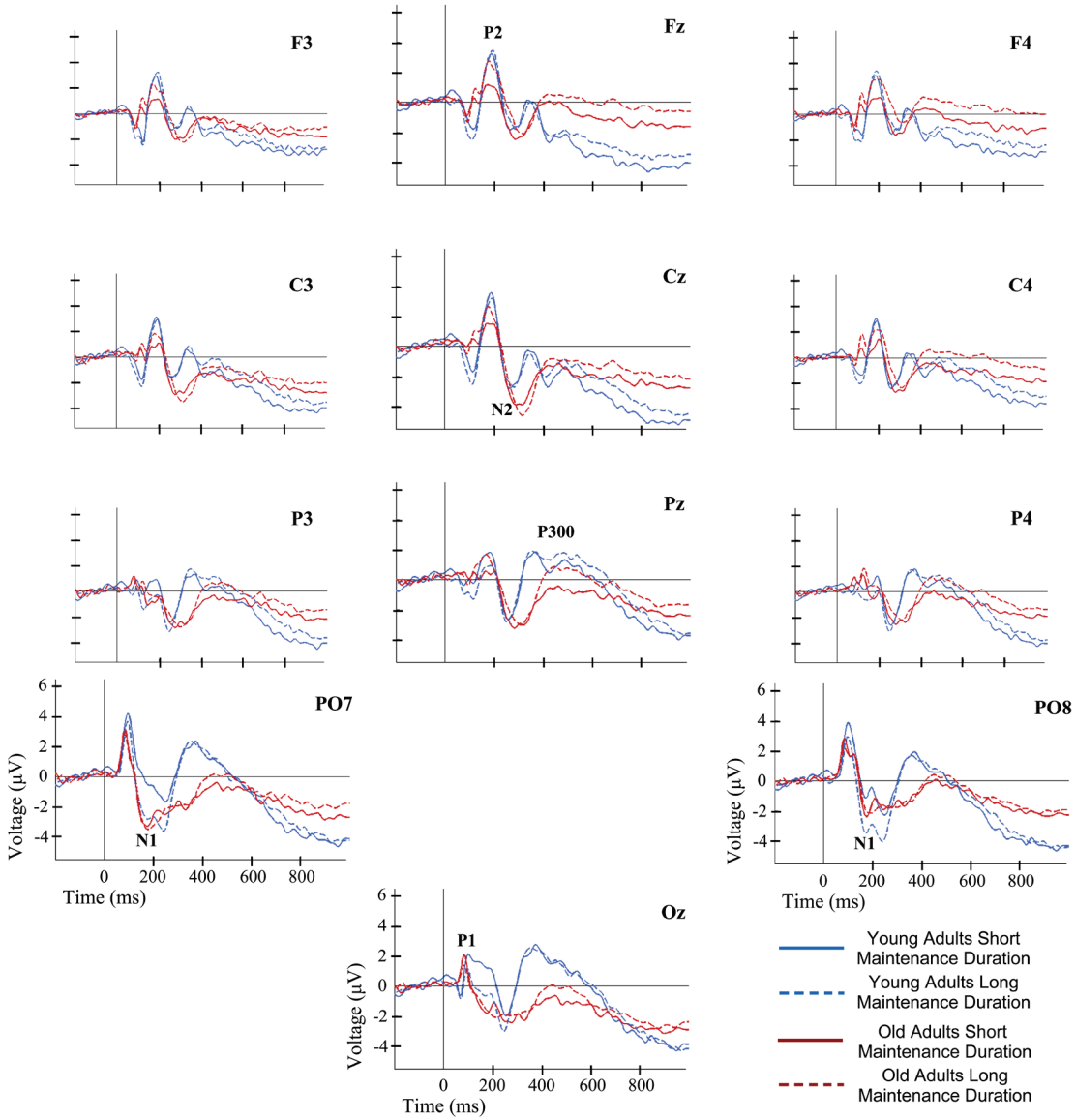
USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

FIGURES


(50 ms)
Prestimulus Interval
500 ms
Encoding
1000 ms
Maintenance
2500 or 5000 ms
Recognition
until response or 3000 ms
Intertrial Interval
800 ms


2200
2000
1800
1600
1400
1200
IES SCORES
LOW
HIGH
MEMORY LOAD
Old Adults
Young Adults


F3
Fz
P2
F4
C3
Cz
N2
C4
P3
Pz
P300
P4
PO7
N1
PO8
N1
Oz
P1
Voltage (μV)
5
3
1
-1
-3
0
200
400
600
800
Time (ms)
Young Adults Low Memory Load
Young Adults High Memory Load
Old Adults Low Memory Load
Old Adults High Memory Load


F3
P2
Fz
F4
C3
Cz
N2
C4
P3
Pz
P300
P4
PO7
N1
PO8
N1
Oz
P1
Voltage (μV)
Time (ms)
0
200
400
600
800
6
4
2
0
-2
-4
Young Adults Short Maintenance Duration
Young Adults Long Maintenance Duration
Old Adults Short Maintenance Duration
Old Adults Long Maintenance Duration

3.5 STUDY 5

Pinal, D., Zurrón, M., Díaz, F. & Sauseng, P. (accepted for publication in Neurobiology of Aging). Stuck in Default Mode: Inefficient Cross-Frequency Synchronization May Lead to Age-Related Short-Term Memory Decline. 10.1016/j.neurobiolaging.2015.01.009.

Este último estudo do presente traballo de doutoramento completa a análise dos efectos do avellentamento na actividade eléctrica cerebral subxacente á MT viso-espacial. Así pois, e posto que o **Estudo 3** e o **Estudo 4** examinaron as fases de codificación e recuperación de información en MT, o obxecto do presente estudo é examinar as diferenzas entre mozos e adultos maiores durante o mantemento de información viso-espacial en MT.

Como puxo de manifesto o **Estudo 2**, a actividade alfa é un aspecto básico do mantemento de información en memoria de traballo. Ademais, compre lembrar que recentemente suxeriuse que a sincronía entre a fase da actividade alfa (8-12 Hz) e a amplitude da actividade gamma (>30 Hz) poderían formar un mecanismo neural ó servizo do mantemento de información en MT. Neste mecanismo a actividade alfa tería un rol inhibidor asociado ó control executivo. Xa que logo, o seu ciclo podería dividirse en dúas metades, unha delas sería unha fase de excitación que sinala os momentos onde á receptividade neural ós "inputs" procedentes doutras rexións é máxima, e na que se debería observar a actividade gamma; en tanto que a outra metade sería inhibidora, e reflectiría períodos nos que a receptividade é mínima e, xa que logo, non se debería observar actividade gamma concorrente. Pola súa banda, o rol de gamma neste mecanismo sería o de representar a información sobre os estímulos. Non obstante, aínda que este tipo de sincronía observouse en pequenos circuítos locais, a súa validez ou presenza en conexións funcionais de longo alcance non foi probada. Así pois, e dado que os adultos maiores presentan un déficit na inhibición da actividade da rede de repouso durante a execución de tarefas de MT, o obxectivo V propúxose analizar a actividade oscilatoria durante o período de mantemento, e contrastar se a relación entre alfa frontal e a actividade oscilatoria rápida de áreas posteriores pode reflectir a coordinación de redes funcionais de longa distancia, e se ese mecanismo está relacionado co antedito déficit inhibitorio e, a súa vez, co declive na execución asociado á idade.

Deste xeito, no **Estudo 5** argumentamos que a través do aniñamento da actividade oscilatoria rápida (gamma) de rexións posteriores na fase excitadora ou inhibidora das ondas alfa da rexión frontal, as redes de longa distancia poden ser eficientemente conectadas ou desconectadas, respectivamente. Polo tanto, esperamos atopar que nos mozos a actividade oscilatoria rápida de rexións posteriores relevantes para a tarefa (rede fronto-parietal) prodúcese ó tempo que a fase excitadora de alfa en frontais; propiciando así a conexión de redes relevantes para a tarefa. Este mecanismo veríase afectado polos

procesos de avellentamento, co que nos adultos maiores a fase excitadora de alfa asociaríase coa actividade oscilatoria rápida de rexións posteriores pertencentes a rede de repouso; estando, a súa vez, este factor relacionado coa peor execución na tarefa.

Co animo de conseguir estes obxectivos e testar as nosas hipóteses, analizouse a actividade oscilatoria cerebral durante o mantemento de información viso-espacial na tarefa de emparellamento demorado correspondente á mostra de 20 mozos e 20 adultos maiores sans usada nos **Estudo 3** e **Estudo 4**. Para iso, estimouse a actividade das fontes xeradoras do sinal EEG recollido no coiro cabeludo a través do software LORETA. En primeira instancia comparouse a potencia de diferentes frecuencias (theta: 4-6 Hz, alfa, beta: 12-20 Hz e 20-30 Hz e gamma) entre ambos grupos e entre ambas condicións de carga para cada grupo. Estas comparacións realizáronse para os datos dunha ventá temporal que se estendeu entre os 2500 e os 4000 ms tras a desaparición do estímulo mostra, xa que este período non ten interferencias de procesos tardíos de codificación e reflicte mecanismos puros de retención da información viso-espacial en MT.

Os resultados desta análise indicaron que a maiores niveis de carga ambos grupos presentaban maior potencia de alfa no córtex frontal. A pesares de que o incremento era máis disperso en adultos maiores que en mozos, o efecto en ámbolos dous grupos solapábase unicamente no córtex cingulado anterior (CCA). Esta rexión forma parte da "salience network", que é unha rede que se encarga de coordinar a actividade entre as redes relevantes para a tarefa e de repouso. Á beira disto, tamén se observaron diferenzas entre ambos grupos na actividade beta e gamma, principalmente, en áreas temporais esquerdas, sendo a potencia maior en adultos maiores que en mozos. A potencia de beta nestas áreas, ademais, correlacionou co tempo de reacción. Polo que este resultado podería indicar diferenzas na estratexia coa que os grupos completaron a tarefa. Nese senso, a estratexia levada a cabo polos maiores tería sido menos eficiente que a dos mozos.

A continuación, e de cara a testar a nosa hipótese, a actividade estimada para as fontes foi concentrada en 21 rexións de interese (RDI), que incluían os vóxeles que mostraron diferenzas entre grupos ou entre condicións de carga en memoria na análise anterior. Entón, a fase de alfa foi rexistrada para a RDI fronto-medial que incluía o CCA, e dividida en 16 porcións que comprendían 22.5º do ciclo de alfa cada unha. A amplitude da actividade oscilatoria rápida de tódalas demais RDIs foi rexistrada, e ordenada en función da fase de alfa na RDI fronto-medial. Cos datos ordenados desta forma, avaliouse a existencia dunha relación significativa entre a fase de alfa frontal e a actividade oscilatoria rápida posterior, e, amais, comparouse a distribución da actividade oscilatoria rápida nas diferentes porcións da fase de alfa entre ambos grupos de idade. Por último, a distribución da actividade oscilatoria rápida nas diferentes porcións da fase de alfa fronto-medial foi correlacionada cos datos de execución (taxa de acertos e tempos de reacción) para aquelas RDIs que mostraron un acoplamento significativo da súa actividade coa fase de alfa fronto-medial.

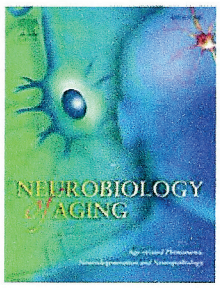
Os resultados destas análises amosaron unha relación de acoplamento significativa para ambos grupos de idade entre a fase de alfa en rexións frontais coa actividade gamma (>50 Hz) en rexións posteriores pertencentes tanto á rede relevante para a tarefa (xiros angular e supramarxinal) como á rede de repouso (precuneus), porén con diferente sentido. Isto é, namentres os mozos mostraban a actividade gamma de rexións relevantes para a tarefa na fase excitadora de alfa, os maiores mostraban dita actividade na fase inhibidora. Pola contra, os mozos presentaban a actividade das rexións pertencentes á rede por repouso durante a fase inhibidora de alfa frontal, en tanto que os adultos maiores facíano durante a fase excitadora de alfa en rexións frontais.

Amais, dita relación de fase e amplitude correlacionou de forma significativa cos datos condutuais de execución na tarefa para ambos grupos de idade e sen diferenzas no valor da correlación entre eles. Así, os participantes nos que a actividade gamma dunha rexión pertencente á rede por repouso (precuneus) acoplábase máis próxima a fase excitadora de alfa presentaban os tempos de reacción máis longos e as menores taxas de acerto na tarefa.

Xa que logo, os resultados obtidos no presente estudo parecen indicar que o acoplamento entre a fase de alfa en rexións frontais e a actividade gamma en rexións posteriores é un mecanismo neural encargado da conectividade funcional e da coordinación de redes corticais de longa distancia. Cabe salientar tamén, que os resultados apuntan que os adultos maiores presentan unha falla de sincronía entre os diferentes nodos da rede relevante para a tarefa, en tanto que manteñen sincronizadas rexións da rede de repouso. Amais, esta falta de desconexión na última das redes semella estar detrás do declive na memoria a curto prazo relacionado coa idade. Así é que estes resultados soportan a idea dunha orquestración ineficiente das redes cerebrais no cerebro humano avellentado e identifican o mecanismo neural responsable desa quebra no control executivo.

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

Accepted Manuscript



Stuck in Default Mode: Inefficient Cross-Frequency Synchronization May Lead to Age-Related Short-Term Memory Decline

Diego Pinal, Montserrat Zurrón, Fernando Díaz, Paul Sauseng

PII: S0197-4580(15)00042-1

DOI: 10.1016/j.neurobiolaging.2015.01.009

Reference: NBA 9189

To appear in: *Neurobiology of Aging*

Received Date: 17 June 2014

Revised Date: 12 January 2015

Accepted Date: 13 January 2015

Please cite this article as: Pinal, D., Zurrón, M., Díaz, F., Sauseng, P., Stuck in Default Mode: Inefficient Cross-Frequency Synchronization May Lead to Age-Related Short-Term Memory Decline, *Neurobiology of Aging* (2015), doi: 10.1016/j.neurobiolaging.2015.01.009.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

This study is in press and has been published online in Neurobiology of Aging. Its complete reference is:

Pinal, D., Zurrón, M., Díaz, F. & Sauseng, P. (in press). Stuck in Default Mode: Inefficient Cross-Frequency Synchronization May Lead to Age-Related Short-Term Memory Decline. 10.1016/j.neurobiolaging.2015.01.009.

Further, this work can be accessed (open access) via the following link:

http://www.neurobiologyofaging.org/article/S0197-4580%2815%2900042-1/fulltext

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

4. General Discussion

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

4.1 TIME COURSE OF BRAIN ACTIVITY DURING ENCODING AND RETRIEVAL IN VISUOSPATIAL WORKING MEMORY

Objective I of this doctoral thesis aimed to determine the time course of brain activity during encoding and retrieval/recognition of visuospatial information in working memory, since there was a lack of a thorough knowledge about the time course of brain activity supporting WM function. This was one of the main weaknesses of neuroscientific approaches to this topic (Baddeley, 2012; Jonides et al., 2008).

Results from **Study 1** of the present work indicated that the time course of brain electrical activity may be highly similar during encoding and retrieval operations in visuospatial working memory. In both cases, the ERP could be decomposed in six different factors, which indexed the time course of the neural processes underlying the recorded ERP. Further, the distribution in the scalp of these components as well as their latency since the presentation of sample or probe stimuli closely matched the canonical components that have been traditionally used in the study of working memory function with the ERP technique. Namely, P1, N1, P2, N2, P300 and a slow wave that was positive during encoding and negative during retrieval.

The reinstatement hypothesis, which was generated in long-term episodic memory research, suggests that successful retrieval of an episode highly benefits from the reenactment of encoding related brain activity (Rugg et al., 2008). This hypothesis found support in neuroimaging research results from tasks of associative memory and task that manipulated encoding conditions or strategies (Johnson and Rugg, 2007; Manelis et al., 2011; Nyberg et al., 2000; Rugg et al., 2008). Also, recent research indicated that some brain oscillatory activity features that are present during encoding are reinstated during retrieval in long-term episodic memory (Hanslmayr and Staudigl, 2014; Wimber et al., 2012). Nevertheless, as highlighted in a recent review (Danker and Anderson, 2010), the question arises whether there exists also a temporal reinstatement of brain activity. Remarkably, the present results indicate that the answer to this question may be affirmative. Thus, the present results may extend the reinstatement hypothesis to the temporal dimension and to WM encoding and retrieval operations.

Nevertheless, despite the time course of both process is composed by similar ERP components, these does not mean that retrieval deterministically reinstates the information processing of encoding operations (see Kent and Lamberts, 2008). That is, the nature of some of the processes reflected by the ERP components is likely to be different during encoding and retrieval. For instance, a slow wave was the sixth component for encoding and retrieval, but it presented different polarity in these two cognitive events. A positive slow wave was present during encoding, which may be an index of the elaboration and active maintenance of information that is carried out after the categorization of the stimulus (García-Larrea and Cézanne-Bert, 1998). In contrast, a negative slow wave was

observed during the retrieval, which may be a correlate of planning and execution of a motor response (Shibasaki and Hallett, 2006) once the stimulus has been categorized. Consequently, despite both components reflect post-categorization processes, such processes are probably of different nature. Some other evidence of the difference in the integration and structure of the processes reflected in the ERP components that comprised the time course of encoding and retrieval is provided by the differential response of these components to memory load manipulations depending on the cognitive event they belong to (discussed in next section).

Accordingly, these results are the first that indicate that the temporal structure of information processing during WM encoding may be reinstated to a certain degree during WM retrieval. Therefore, they may constitute a first step in order to strengthen neurobiological WM theories with a detailed description of the time course of brain activity supporting encoding and retrieval.

4.2 MEMORY LOAD AND MAINTENANCE DURATION EFFECTS ON BRAIN ELECTRICAL ACTIVITY SUPPORTING VISUOSPATIAL WORKING MEMORY

Once the time course of brain electrical activity (as revealed by ERPs) during encoding and retrieval was objectively determined. Objective II of the present doctoral work aimed to assess the effects that memory load and/or the duration of the maintenance period have on the different ERP components identified during visuospatial WM encoding and retrieval, since previous research indicated that both factors may limit the capacity of WM (Alvarez and Cavanagh, 2004; Bays and Husain, 2008; Cornelissen and Greenlee, 2000; Gold et al., 2005; Luck and Vogel, 1997; Zhang and Luck, 2008). Moreover, previous research showed partly contradictory results regarding the modulation of different components by memory load (e.g. Morgan et al., 2008; Soria Bauser et al., 2011); while the effects of maintenance duration were only tested for N2 (van der Ham et al., 2010).

4.2.1 Memory load effects

Results of the effects of memory load on behavioral performance showed that high memory load was associated with lower accuracy rates and longer reaction times than low memory load. Inverse Efficiency scores (see **Study 1**) also reveal a poorer performance in high than low memory load. Consequently, results are in accordance with previous findings (Alvarez and Cavanagh, 2004; Luck and Vogel, 1997) and supports the idea that cognitive demands and task difficulty can be increased with memory load.

Regarding brain activity, results revealed that early components of the ERPs, i.e. P1 and N1, are insensitive to memory load manipulations during encoding as well as retrieval in the present DMS task. The cortical sources for these components have been located in posterior cortical brain regions (Di Russo et al., 2001), which has been considered as a marker of the relation of these components with perceptual processing (Luck et al., 1990;

Vogel and Luck, 2000). Thus, it seems that the number of dots inside a domino do not change the way the tile is perceived. However, this view was challenged by LORETA results, which showed a memory load dependent reduction of medial frontal gyrus and anterior cingulate cortex activation early in the time course of encoding and retrieval (i.e. concurrent with P1 and N1 amplitude peaks as recorded at the scalp). Some authors suggest that these regions are part of the default mode network (Raichle and Snyder, 2007), which has been shown to reduce its activation in a cognitive-effort dependent fashion (Tomasi et al., 2006). Consequently, results may indicate that the increased demands on perceptual processing due to high memory load conditions are compensated by modulations of brain activation in frontal cortical regions while preserving posterior resources unaltered.

Besides this, during visuospatial WM encoding and retrieval, memory load effects were observed for P300 component. Lower P300 amplitudes in high than low memory load were found. Similar reductions of P300 amplitude with memory load are a common finding in WM research (Kok, 2001, 1997). Indeed, this has been related to increases in task difficulty (Kok, 2001; Wijers et al., 1989), a fact that is corroborated by behavioral results in the present work. Several authors have suggested that this memory load dependent reduction of P300 amplitude may reflect that fewer processing resources are available for stimulus categorization (McEvoy et al., 1998; Morgan et al., 2008). Further, these authors indicate that such reduction in the availability of resources could be due to a greater distribution of processing resources, which are allocated to other processes beside stimulus categorization when memory load is high.

Remarkably, close in time to P300 amplitude modulations, memory load also affected the positive slow wave during encoding and N2 during retrieval. Both components showed larger amplitude in high than low load conditions. Accordingly, present results may indicate that the greater demand generated by high memory load conditions reduced the resources available for stimulus categorization, probably due to a redistribution of processing resources towards elaboration and maintenance of information during encoding and towards stimulus evaluation during retrieval. Further, in the same time window as N2 during retrieval, greater activation was observed in Brodmann area (BA) 10 for high than low load trials. This area is supposed to coordinate the integration of internal and external information (Christoff and Gabrieli, 2000; Ramnani and Owen, 2004), a process needed for the comparison of the probe stimuli with the memory template. Such comparison is thought to be a subprocess of stimulus evaluation that could be reflected by N2 (Yin et al., 2011). Therefore, these results may add support for a different distribution of processing resources depending on memory load.

Interestingly, memory load effects on ERP components timing was restricted to P300 latency during retrieval, which was longer for high than low memory load trials. This is also a common finding in P300 research (for review see Polich, 2007; Verleger, 1997).

Some authors have suggested that P300 latency is an index of the time required to evaluate a stimulus (Kutas et al., 1977; Magliero et al., 1984). Thus, this may indicate that longer time is needed to categorize the stimulus due to greater demands exerted by high memory load trials only during the retrieval and recognition of information held in visuospatial WM.

4.2.2 Maintenance duration effects

In contrast to memory load, maintenance duration has no effects on behavioral performance. Furthermore, this was at odds with expectations based on time-based decay theories, and with reports from previous studies that used similar durations of the maintenance period, but different visuospatial stimuli -i.e. the position of a dot in relation with a cross- (van der Ham et al., 2007).

Nonetheless, results revealed that maintenance duration modulated brain activation early in the time course of information retrieval/recognition (160-200 ms). Thus, higher activation was found at the left middle temporal gyrus for long than short maintenance periods. Additionally, longer durations of the maintenance period were related to larger N2 amplitudes. This latter result is in accordance with previous findings (van der Ham et al., 2010). Therefore, present results extends the effects observed for maintenance duration manipulations, and may confirm previous assumptions, which posit that increases in the duration of the maintenance period increase the demands on WM cognitive capacity (Barch et al., 1997; Gold et al., 2005). Particularly, the present results may indicate that long maintenance durations are associated with a greater allocation of resources to perceptual and stimulus evaluation processes that support the comparison and recognition of the target among the different alternatives presented as part of the probe stimulus.

It is noteworthy, that shorter P300 latencies were observed after long than short maintenance periods. This effect may reflect the fact that after long maintenance periods participants have less uncertainty about the moment in time in which the probe stimuli will be presented and, in turn, this would generate a lower jitter in the response to the stimuli (see Sutton et al., 1967 for a similar argumentation). However, this explanation remains speculative. Consequently, future work that tries to deepen the understanding of maintenance duration effects is warranted.

The last two sections have discussed the effects of memory load and maintenance duration on visuospatial WM. In summary, it seems that high memory load was associated with increased cognitive demands and task difficulty. These increases may be compensated with a memory load dependent reduction of activation in frontal regions of the default mode network, particularly early in the time course of encoding and retrieval processes, which is concurrent to preserved perceptual processing. Additionally, allocation of resources is modulated by memory load. Specifically, it seems that increased demands due to high memory load are related to a redistribution of processing resources, reducing those

available for stimulus categorization while increasing those gathered by elaboration and active maintenance during encoding and by stimulus evaluation during retrieval. Also, higher levels of memory load increase the time required to complete stimulus evaluation during retrieval. In contrast, maintenance duration effects were complex. Hence, in the absence of modulation of behavioral performance, brain activity revealed a larger allocation of resources to perceptual as well as stimulus evaluation processes after long than short maintenance periods. However, stimulus categorization was slower in the short maintenance period condition. Consequently, despite these results extend previous knowledge about the effects of maintenance duration on the ERPs during retrieval; still further work is needed to thoroughly understand them.

4.3 BRAIN OSCILLATORY DYNAMICS AND THEIR MODULATION BY MEMORY LOAD DURING THE MAINTENANCE OF VISUOSPATIAL INFORMATION IN WORKING MEMORY

Study 1 addressed basic aspects of visuospatial WM related to encoding and retrieval brain activity. To complement this, **Study 2** focused on brain electrical activity during the maintenance period. In particular, Objective III of this doctoral thesis aimed to examine the dynamics of oscillatory alpha activity during the maintenance of visuospatial information in WM and their modulation by memory load. Further, since there is certain controversy regarding alpha band dynamics in response to high memory load due to opposing results of previous studies (Busch and Herrmann, 2003; Gevins et al., 1997; Scheeringa et al., 2009; Stipacek et al., 2003; Tuladhar et al., 2007); **Study 2** analyses were focus on testing whether different cortical regions concurrently shows different alpha dynamics during information maintenance in human participants and how this dynamics were modulated by memory load.

Results from these analyses indicated that oscillatory dynamics during the maintenance period of the DMS task were characterized by an increase of alpha power in parieto-occipital regions as well as by an increased alpha phase synchronization of these regions, as compared to the baseline period (i.e. a window of 500 ms prior to warning tone onset). Estimations of source activity located this alpha dynamics to right cuneus, right paracentral lobe and bilateral precuneus/posterior cingulate cortex, which are thought to be task-irrelevant posterior regions (see Fransson & Marrelec, 2008). Therefore, in accordance with previous interpretations (e.g. Jokisch and Jensen, 2007), this increased alpha activity may signal the disengagement of task irrelevant regions, thus protecting relevant neural representations of being disrupted by irrelevant information. Accordingly, the present results support the role of alpha activity in the executive control of information processing (Freunberger et al., 2011; Sauseng et al., 2009), and, in particular, as a director of the flow of information to task relevant cortical regions (Jensen and Mazaheri, 2010; Klimesch et al., 2007).

In addition, memory load modulate this alpha dynamics during the maintenance of visuospatial information in WM. Relative to low memory load trials, high memory load trials presented lower alpha synchronization in posterior parietal regions, as well as higher alpha desynchronization in prefrontal cortex. These modulations of alpha activity were located at right precentral and superior and inferior parietal gyri as well as on left middle frontal gyrus. All these cortical regions are supposed to be part of the fronto-parietal network underlying WM function (Cabeza and Nyberg, 2000; Linden, 2007). Accordingly, alpha decreases with memory load probably reflect a release of inhibition in these cortical regions (Gevins et al., 1997), or, in other words, a more extensive recruitment of resources from regions within the fronto-parietal network as WM demand increase. Therefore, taken together with results from ERP analysis during encoding and retrieval, it seems clear that memory load modulated processing resources in the fronto-parietal network along the three cognitive events comprised in visuospatial WM function.

Furthermore, interregional synchronization of alpha phase was also modulated by memory load manipulations during information maintenance. Specifically, alpha phase synchrony between left inferior parietal lobe and left middle frontal gyrus and anterior cingulate cortex was lower in high than in low memory load conditions. Further, the analysis of cross-correlation between the two signals revealed that left middle frontal gyrus alpha phase leads that of inferior parietal lobe by 15 ms. These results are consistent with the role of alpha activity in top-down executive control of information processing in posterior cortex (Sauseng et al., 2011), although some caution must be taken until confirmed by future analysis with techniques that enable the assessment of causal relations between two signals (e.g Granger Causality).

Taken together, these results remark the importance of alpha dynamics for information maintenance in visuospatial WM and highlighted the role of interregional synchrony in the alpha band for the successful functioning of WM, supporting the role that interregional synchronization of neural populations (as revealed by oscillatory activity) may play in superior cognitive capacities like WM (Buzsáki, 2006; Zimmer, 2008). Further, the effects of memory load on alpha dynamics revealed that this factor may modulate the recruitment of processing resources in the task-relevant as well as in the task-irrelevant networks from information encoding to information retrieval, through information maintenance. Also, they may indicate, for the first time, that different memory load dependent alpha dynamics can coexist in different cortical regions, while all of them participate in the executive control of information processing. In particular, alpha power increases in task-irrelevant regions during maintenance relative to a baseline period may reflect an increase of inhibition that aids to direct the flow of information to task-relevant regions. These latter regions showed a concurrent memory load dependent decrease of alpha activity, which probably reflects a reduction in the level of inhibition as cognitive demand increases. In addition, the reduced frontal to parietal alpha synchronization may be an index of a parietal release of inhibitory top-down executive control processes exerted by frontal regions.

4.4. IMPACT OF AGING ON BRAIN ACTIVITY DURING ENCODING AND RETRIEVAL OF INFORMATION IN VISUOSPATIAL WORKING MEMORY

So far, the general discussion of this doctoral work has focused on objectives related to general basic aspects of brain electrical activity supporting visuospatial WM, as well as the effects of memory load and maintenance duration on this activity. Such objectives are supposed to be basic for a better understanding of visuospatial WM function. Nevertheless, a thorough understanding of this process is only one of the two columns in which this work is supported. Indeed, the main interest of this doctoral work is on age-related changes in this cognitive capacity, as it may be a crucial factor for cognitive integrity and quality of life in old adults. Therefore, the present and the following sections will address the impact of aging on the ERP components identified as main factors of the time course of encoding and retrieval processes, and on the oscillatory activity during the maintenance of information.

Accordingly, objective IV of this doctoral thesis aimed to analyze age-related effects and their interaction with those of memory load and maintenance duration during encoding and retrieval. Such analysis will help to shed light on the extent to which the hypothesized age-related generalized slowing of processing speed (Salthouse, 1996) and working memory capacity reduction (Craik and Byrd, 1982; Park, 2000) are applicable to these cognitive events.

4.4.1 Effects on behavioral performance

Results revealed that old adults had poorer performance than young adults in the DMS tasks. Indeed, they presented longer reaction times and lower accuracy rates; which add support to age-related slowing of processing speed and reduced working memory capacity hypotheses of aging. In further support of the latter, results showed that old adults' accuracy rates were lower in high than low load conditions while no such effect was found in young adults. It is noteworthy too, that results of analyses run with IE scores showed the same pattern. Consequently, age-related effects as well as their interaction with memory load effects on behavioral performance may not stem from differences in the stability of the response criterion or in speed-accuracy trade-offs. In contrast, maintenance duration did not interact with age-related effects on behavioral performance.

Consequently, behavioral results may indicate that visuospatial WM suffer an age-related decline. This decline seems to be associated with a slowing of processing speed and with a greater sensitivity of old adults to cognitive demands, particularly, to WM load. The latter, is possibly reflecting a reduced capacity of WM with age.

4.4.2 Effects on ERP components latency

As regards age-related effects on the latency of ERP components, results did not find any effects of age on P1 or N1 during encoding nor during retrieval. This may indicate that

the perceptual processing usually associated with these components is preserved in the aged human brain. Further, these results are at odds with the predictions of the generalized slowing of processing speed hypothesis of aging.

Nonetheless, longer P2 and N2 latencies for old than young adults during encoding as well as longer N2 and P300 latencies during retrieval were observed. Accordingly, these results may indicate that age-related slowing is confined to specific processes within the time course of encoding and retrieval in WM. Interestingly, the processes affect by the age-related slowing seem to depend on the cognitive event that is explored. Thus, during encoding, detection of relevant features and evaluation of relevant stimuli were slowed with age, as reflected by P2 (Luck and Hillyard, 1994; Potts, 2004) and N2 latencies (Folstein and van Petten, 2008), respectively. In contrast, during retrieval, slowing may affect the evaluation of relevant stimuli and their categorization, as reflected by N2 and P300 latency, respectively.

Remarkably, N2 latency during encoding was associated with response accuracy, thus, the longer N2 latency, the higher the accuracy. This relation was especially marked in old adults. This may indicate that old adults need more time to successfully complete the evaluation of the sample stimulus. Further, that older adults benefit when they have or spent more time to complete a task is a well in line with the age-related slowing of processing speed hypothesis. Moreover, this result highlights the importance of encoding processes for a successful completion of WM tasks like the DMS.

It is also noteworthy that there was no interaction between age-related and memory load dependent or maintenance duration dependent effects on ERP components latency. As a result, ERP components latency results do not offer support for hypothesis suggesting a greater sensitivity of old adults to cognitive demands.

Taken together, the results of the present work may nuance the generalized slowing of processing speed hypothesis to explain age-related declines in WM. Thus, it seems that perceptual processes are preserved in old adults, but that there exist a specific slowing of processing on later components of the time course of encoding and retrieval. The specific processes showing this age-related slowing may depend on the nature of the cognitive event that is being explored. For instance, in the present task, age-related slowing was specific for detection and evaluation of the properties of the to be encoded visuospatial stimuli, and for evaluation and categorization of visuospatial stimuli during retrieval and recognition in WM. Remarkably, correlational analyses revealed that this age-related slowing during encoding may be associated with behavioral performance, especially in older adults. This relation points to a benefit in behavioral performance for those old adults that take more time to evaluate the stimuli they were encoding in WM. Consequently, this association between N2 latency and reaction times also supports age-related slowing of processing theories.

4.4.3 Effects on ERP components amplitude

As regards ERP components amplitude, results revealed only main effects of age during encoding of visuospatial information in WM. Old adults showed lower P2, P300 and PSW amplitudes than young adults during this cognitive event. This pattern of results may indicate that there is a reduction in the resources allocated to the top-down evaluation of the relevant features of a stimulus and to stimulus categorization, which are supposed to be reflected on P2 (Wang et al., 2010) and P300 (Kok, 2001, 1997) amplitudes, respectively. Additionally, the lower amplitude of the positive slow wave in old than young adults may also indicate a reduction of resources allocated to post-categorization processes, which are probably associated with the elaboration and active maintenance of information in WM (García-Larrea and Cézanne-Bert, 1998). Consequently, these results offer support to the suggested age-related reduction of processing resources (Craik and Byrd, 1982; Craik and Rose, 2012).

In contrast, interactions between the effects of age and those of memory load or maintenance duration were only found during visuospatial information retrieval/recognition. That is, in high load conditions young adults showed a more homogenous distribution of P300 amplitude than in low load conditions; thus, lacking the characteristic parietal maximum observed in the latter condition. Old adults presented such homogenous scalp distribution of P300 amplitude in both memory load conditions. Interestingly, in line with previous results (Banich, 1998; Reuter-Lorenz and Cappell, 2008; Reuter-Lorenz et al., 1999) young adults seem to compensate for increased cognitive demands through a greater reliance on frontal relative to parietal resources. However, older adults seem to have a greater reliance on frontal relative to posterior resources already at low memory load. Similar findings in long-term episodic memory studies led some authors to suggest the existence of a posterior to anterior shift of brain activity with aging ([PASA], Davis et al., 2008). Hence, these results may extend the PASA hypothesis to WM retrieval/recognition processes. Additionally, they may offer support for the neurocognitive scaffolding theory, which suggests that compensatory mechanisms for increased cognitive demands are common along the lifespan, but that old adults rely on such mechanism at lower levels of demands than young adults due to their reduced working memory capacity and greater sensitivity to memory load (Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Park, 2010).

Taken together, the analyses of the impact of aging on brain activity during visuospatial information encoding and retrieval/recognition in WM revealed that: i) perceptual processes seem to be preserved in healthy aging. ii) There is an age-related slowing that specifically affects relevant features detection and stimulus evaluation during encoding and evaluation and categorization of visuospatial stimuli during retrieval. iii) There is an age-related decrease in the amount of processing resources allocated to relevant features detection and stimulus categorization as well as elaboration and active

maintenance of information during encoding. iv) It is likely that the old adults have a greater reliance than young adults in frontal relative to posterior resources, extending the PASA hypothesis to WM recognition operations. v) Old adults may be more sensitive than young adults to WM load, as they show higher pernicious effects of memory load on behavioral performance as well as signs of cognitive effort (more homogenous distribution of P300) at lower levels of demand than young adults. This also offers support to the neurocognitive scaffolding hypothesis.

4.5 IMPACT OF AGING ON BRAIN OSCILLATORY DYNAMICS DURING THE MAINTENANCE OF VISUOSPATIAL INFORMATION IN WORKING MEMORY

Section 4.4 has reviewed and discussed results from **Study 3** and **Study 4**, which focused on the impact of aging on encoding and retrieval brain electrical activity. Therefore, this last section will address age-related changes in brain electrical activity during the maintenance of visuospatial information in WM. Indeed, Objective V of this doctoral thesis aimed to explore age-related changes of oscillatory activity during maintenance of information as well as their modulation by memory load. Further, especial emphasis was made on test whether inter-regional phase:amplitude coupling of alpha and fast oscillatory activity could be a neural mechanisms supporting the orchestration of long-range brain functional networks and the maintenance of information in working memory, and if this mechanism was also modulated by the age of the participants.

In particular, given that alpha phase coupling with gamma amplitude has been suggested as a lynchpin of neural processing supporting maintenance of information in WM (Roux and Uhlhaas, 2014) and that old adults showed an inefficient balance of the fronto-parietal and default mode networks activation during task execution (Park et al., 2010; Sambataro et al., 2010), we hypothesized that: i) interregional cross-frequency synchronization of this two frequency bands activity may be a neural mechanisms supporting the active engagement and disengagement of long-range functional networks; and ii) that such mechanism may be altered with age allowing the engagement of the default mode network during information maintenance, and in turn, being associated with age-related declines in task execution (for details see Introduction, p. 20).

Results from spectral power analysis during the maintenance of information showed higher activity in beta (12-20 Hz and 20-30 Hz) and gamma (30-50 Hz) bands at left temporal regions for old than for young adults. These increases may indicate that more effort was applied by old than by young adults to successfully complete the task (for similar interpretations of beta and gamma increases see Howard et al., 2003; Posada et al., 2003). However, an alternative explanation for this increase in activity of temporal areas is that they may indicate an inefficient and dedifferentiated recruitment of posterior resources in old adults (see Carp et al., 2011; Goh, 2011) during the maintenance of visuospatial information in WM, as reflected by a positive correlation between beta (20-30 Hz) power

in these regions and reaction time. Accordingly, future work is needed to clarify the implications of power spectral activity in the beta band of posterior cortical regions during information maintenance.

In addition, results revealed a memory load dependent increase of alpha power in frontal regions for both groups. Interestingly, despite the increase was spatially more widespread in old adults (not significantly), it overlapped for both groups only in the anterior cingulate cortex (ACC). This latter region is considered part of the salience network and, therefore, may participate in the switch between fronto-parietal and resting-state functional networks activation (Seeley et al., 2007; Sridharan et al., 2008). Taken together with the inefficient age-related increase of beta power in temporal regions, the present spectral power results may indicate that old adults has a greater reliance than young adults on frontal relative to posterior resources, in accordance with and extending the PASA hypothesis.

Remarkably, results from the phase:amplitude coupling analysis revealed that alpha phase from the ACC was significantly coupled with gamma activity from angular and supramarginal gyri and from precuneus. Angular and supramarginal gyri are considered part of the fronto-parietal task related network, since they are active when memory contents are the focus of attention (Cabeza et al., 2008; Ciaramelli et al., 2008). Whereas the precuneus is thought to be a central node of the resting state network (Fransson and Marrelec, 2008). This confirms the role of inter-regional alpha phase coupling with posterior gamma amplitude in the coordination of long-range functional networks.

Further, in line with our hypothesis, the preferred phase angle of frontal alpha activity for the coupling of posterior gamma activity from task-relevant and resting state related regions was different in young and old adults. Indeed, young adults gamma activity in angular/supramarginal gyri was stronger when alpha phase expressed a trough, while gamma amplitude in precuneus occurred predominately shortly after the peak. This pattern was reversed in old adults. Given that previous work has pointed to alpha trough as the excitatory part of the alpha cycle (Haegens et al., 2011), the present results may suggest that young adults engage task-related functional networks while old adults connect resting state related regions during the maintenance of visuospatial information in WM. Remarkably, poorer accuracy rates and longer RTs were associated with precuneal gamma amplitude being locked towards the trough of frontal alpha; which is the characteristic pattern of older adults. Accordingly, it appears as if inefficient functional connectivity between fronto-medial regions and precuneus is, at least in part, responsible for the STM decline observed in elderly participants. Therefore, this data also offer support to inhibitory deficit theories of aging (Gazzaley and D'Esposito, 2007; Hasher and Zacks, 1988), since default mode network activity should be inhibited during task execution.

In summary, results highlighted age-related differences in the recruitment of posterior resources. Furthermore, both groups showed a similar response to increased cognitive

demands, which supports neurocognitive scaffolding theories. Also, old adults seem to have a greater reliance than young adults in frontal relative to posterior resources, which supports PASA hypothesis. Finally, interregional alpha phase to gamma amplitude coupling results confirm the role of this mechanism in the coordination of long-range functional networks in the brain. This oscillatory synchrony mechanism might be altered in old adults, enabling the engagement of default mode activity during task execution, a fact associated with poorer performance. Therefore, this inefficient phase:amplitude coupling in old relative to young adults may be seen as an index of a deficit in inhibitory function mediating age-related declines in visuospatial WM.

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

5. Conclusions

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

This work was devoted to the study of visuospatial WM and the impact of healthy normal aging in this cognitive capacity. For that purpose, participants in the different experimental studies included in this work were asked to memorize the spatial configuration of several spots inside domino tiles that varied in the number and location of the spots they contained, retain this information in memory for a variable and relatively brief period of time, and recognize the retained domino among three alternatives (retrieval/recognition stage) to successfully complete the trials of the experimental task. Electroencephalographic as well as behavioral performance data were analyzed trying to deepen present knowledge about basic aspects of visuospatial working memory, such as the temporal structure of brain activity underlying this capacity or the modulations produced by variations in memory load and/or in the time length of the maintenance period. Also, age-related differences in these basic aspects were addressed in the experimental studies that comprise this doctoral thesis.

Therefore, on the one hand, results of the analyses carried out to shed light on some basic aspects of visuospatial WM drive us to conclude that:

1. The temporal structure of the ERPs during visuospatial WM retrieval/recognition resembles that of encoding. Accordingly, both cognitive events are indexed by six ERP components (i.e. P1, N1, P2, N2, P300 and a slow wave) with similar latencies and scalp distributions.

2. Alpha band oscillatory activity and its different dynamics (i.e. spectral modulation and synchronization) have a key role for visuospatial information maintenance in WM. Further, interregional frontal alpha phase:amplitude coupling with posterior gamma amplitude constitutes a neural mechanism that enables the functional engagement and disengagement of long-range brain networks during the maintenance of information.

3. High memory load increase cognitive demands and task difficulty, which is associated with poorer performance on visuospatial WM tasks.

4. Increased demands imposed by high memory load conditions in the DMS task modulate the recruitment of resources from the fronto-parietal and default mode functional networks. Specifically, it reduces the activation of frontal regions of the resting state network during encoding and retrieval, as well as it reduces the inhibition of task-relevant brain regions through top-down executive control processes during maintenance.

5. High memory load is also related to a redistribution of the available processing resources. This redistribution is associated with a reduction of processing resources available for stimulus categorization in favor of elaboration and active maintenance during encoding and of stimulus evaluation during WM retrieval.

6. Lengthen of the maintenance duration is related to an increase in the allocation of resources to perceptual as well as to stimulus evaluation processes during information retrieval, in the absence of behavioral performance modulations.

On the other hand, results from analyses designed to test the impact of aging on visuospatial working memory led us to conclude that:

7. Normal aging is accompanied by a decline in visuospatial working memory, which is reflected in poorer performance in experimental tasks.

8. Healthy aging is related to a slowing of processing speed that is restricted to evaluation of relevant features and stimuli during encoding and to evaluation and comparison of stimuli during retrieval.

9. There is a lower amount of processing resources available and/or allocated to the detection of relevant features of a stimulus as well as for categorization and post-categorization processes with increasing age during encoding.

10. Normal aging is accompanied by a greater reliance in frontal relative to posterior resources during retrieval/recognition. This extends the posterior to anterior shift with aging (PASA) hypothesis to this cognitive event of visuospatial WM.

11. Old adults show signs of cognitive effort at lower levels of memory load than young adults. Also, in contrast to young adults' performance, task performance decreases in a memory load dependent fashion in old adults. Both facts support an age-related reduction in the capacity of WM as well as the neurocognitive scaffolding hypothesis.

12. Healthy aging is associated with altered alpha phase to gamma amplitude coupling in long range functional networks, which indicates an inhibitory deficit manifested as an inefficient engagement of default mode network (DMN) activity during the maintenance of visuospatial information in WM. Furthermore, this inefficient engagement of DMN activity underlies the age-related behavioral decline.

6. Future studies

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

Despite some conclusions have been drawn from the results of the present set of experimental studies, there are some topics that still need future work to be clarified, as well as some new questions that arise from the results and conclusions itself. Some examples of these subjects for future work are listed below:

- As regards maintenance duration impact on brain electrical activity during WM retrieval/recognition, mixed results were found. Therefore, a complex picture of main effect and interactions could be built from the experimental studies results. Future work controlling factors such as the strategies used by the participants, and presenting shorter as well as longer maintenance periods than those used in the present work would provide useful data to clarify the relation of maintenance period duration with WM demands and brain activity during WM retrieval/recognition.

- Given that frontal hyperactivations in old relative to young adults have been considered an index of compensatory mechanisms, it will be desirable to address the relation between the increased reliance on frontal versus parietal resources of the old adults and behavioral performance. Further, it will be interesting to evaluate the potential cortical sources of that activity.

- Interregional coupling between anterior cingulate and medial frontal alpha activity with posterior gamma activity from task-related and resting state related regions has been revealed as a key mechanism in the orchestration of functional networks during the maintenance of visuospatial information in WM. Therefore, future works should address this kind of cross-frequency coupling with analysis and techniques that allow causal relationships to be investigated. Additionally, it would be of great interest to assess the potential role of this mechanism in pathological aging conditions such as mild cognitive impairment and dementia of the Alzheimer type.

- Further, it will also be of great interest to made a longitudinal study that assesses the potential of the age-related differences revealed in the present doctoral thesis as markers of future cognitive function or even as potential early markers of the future development of pathological aging conditions.

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

7. References

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

Akalin Acar, Z., & Makeig, S. (2013). Effects of forward model errors on EEG source localization. *Brain Topography*, *26*(3), 378–396. doi:10.1007/s10548-012-0274-6

Alvarez, G. A., & Cavanagh, P. (2004). The capacity of visual short-term memory is set both by visual information load and by number of objects. *Psychological Science*, *15*(2), 106–111. doi:10.1111/j.0963-7214.2004.01502006.x

Amenedo, E., & Díaz, F. (1998). Effects of aging on middle-latency auditory evoked potentials: a cross-sectional study. *Biological Psychiatry*, *43*(3), 210–219. doi:10.1016/S0006-3223(97)00255-2

Amenedo, E., Lorenzo-López, L., & Pazo-Alvarez, P. (2012). Response processing during visual search in normal aging: the need for more time to prevent cross talk between spatial attention and manual response selection. *Biological Psychology*, *91*(2), 201–211. doi:10.1016/j.biopsycho.2012.06.004

Anderson, D. E., Vogel, E. K., & Awh, E. (2011). Precision in visual working memory reaches a stable plateau when individual item limits are exceeded. *The Journal of Neuroscience*, *31*(3), 1128–1138. doi:10.1523/JNEUROSCI.4125-10.2011

Andrews-Hanna, J. R., Snyder, A. Z., Vincent, J. L., Lustig, C., Head, D., Raichle, M. E., & Buckner, R. L. (2007). Disruption of large-scale brain systems in advanced aging. *Neuron*, *56*(5), 924–935. doi:10.1016/j.neuron.2007.10.038

Arking, R. (2006). *Biology of aging: observations and principles* (3rd ed., p. 604). New York: Oxford University Press.

Awh, E., Barton, B., & Vogel, E. K. (2007). Visual working memory represents a fixed number of items regardless of complexity. *Psychological Science*, *18*(7), 622–628. doi:10.1111/j.1467-9280.2007.01949.x

Azizian, A., Freitas, A. L., Watson, T. D., & Squires, N. K. (2006). Electrophysiological correlates of categorization: P300 amplitude as index of target similarity. *Biological Psychology*, *71*(3), 278–288. doi:10.1016/j.biopsycho.2005.05.002

Babiloni, C., Babiloni, F., Carducci, F., Cappa, S. F., Cincotti, F., Del Percio, C., … Rossini, P. M. (2004). Human cortical rhythms during visual delayed choice reaction time tasks. A high-resolution EEG study on normal aging. *Behavioural Brain Research*, *153*(1), 261–271. doi:10.1016/j.bbr.2003.12.012

Baddeley, A. (1998a). The central executive: a concept and some misconceptions. *Journal of the International Neuropsychological Society*, *4*(5), 523–526. doi:10.1017/S135561779800513X

Baddeley, A. (1998b). Working memory. *Comptes Rendus de l'Académie Des Sciences - Series III - Sciences de La Vie.*, *321*(2-3), 167–173. doi:10.1016/S0764-4469(97)89817-4

Baddeley, A. (2000). The episodic buffer: a new component of working memory? *Trends in Cognitive Sciences*, *4*(11), 417–423. doi:10.1016/S1364-6613(00)01538-2

Baddeley, A. (2003). Working memory: looking back and looking forward. *Nature Reviews. Neuroscience*, *4*(10), 829–839. doi:10.1038/nrn1201

Baddeley, A. (2012). Working Memory: Theories, Models, and Controversies. *Annual Review of Psychology*, *63*(12), 12.1–12.29. doi:10.1146/annurev-psych-120710-100422

Baddeley, A., & Hitch, G. (1974). Working Memory. *Psychology of Learning and Motivation*, *8*, 47–89. doi:10.1016/S0079-7421(08)60452-1

Baltes, P. B. (1993). The aging mind: potential and limits. *The Gerontologist*, *33*(5), 580–594. doi:10.1093/geront/33.5.580

Baltes, P. B., Staudinger, U. M., & Lindenberger, U. (1999). Lifespan psychology: theory and application to intellectual functioning. *Annual Review of Psychology*, *50*, 471–507. doi:10.1146/annurev.psych.50.1.471

Banich, M. T. (1998). The missing link: the role of interhemispheric interaction in attentional processing. *Brain and Cognition*, *36*, 128–157. doi:10.1006/brcg.1997.0950

Barch, D. M., Braver, T. S., Nystrom, L. E., Forman, S. D., Noll, D. C., & Cohen, J. D. (1997). Dissociating working memory from task difficulty in human prefrontal cortex. *Neuropsychologia*, *35*(10), 1373–1380. doi:10.1016/S0028-3932(97)00072-9

Baudena, P., Halgren, E., Heit, G., & Clarke, J. M. (1995). Intracerebral potentials to rare target and distracter auditory and visual stimuli. III. Frontal cortex. *Electroencephalography and Clinical Neurophysiology*, *94*, 251–264. doi:10.1016/0013-4694(95)98476-O

Bays, P. M., & Husain, M. (2008). Dynamic shifts of limited working memory resources in human vision. *Science*, *321*(5890), 851–854. doi:10.1126/science.1158023

Berens, P. (2009). CircStat: a MATLAB toolbox for circular statistics. *Journal of Statistical Software*, *31*(10), 1–21.

Berryhill, M. E., & Olson, I. R. (2008). The right parietal lobe is critical for visual working memory. *Neuropsychologia*, *46*(7), 1767–1774. doi:10.1016/j.neuropsychologia.2008.01.009

Binder, J. R., Frost, J. A., Hammeke, T. A., Cox, R. W., Rao, S. M., & Prieto, T. (1997). Human brain language areas identified by functional magnetic resonance imaging. *The Journal of Neuroscience*, *17*(1), 353–362.

Bledowski, C., Prvulovic, D., Hoechstetter, K., Scherg, M., Wibral, M., Goebel, R., & Linden, D. E. J. (2004). Localizing P300 generators in visual target and distractor processing: a combined event-related potential and functional magnetic resonance imaging study. *The Journal of Neuroscience*, *24*(42), 9353–9360. doi:10.1523/JNEUROSCI.1897-04.2004

Bokura, H., Yamaguchi, S., & Kobayashi, S. (2001). Electrophysiological correlates for response inhibition in a Go/NoGo task. *Clinical Neurophysiology*, *112*(12), 2224–2232. doi:10.1016/S1388-2457(01)00691-5

Bollimunta, A., Chen, Y., Schroeder, C. E., & Ding, M. (2008). Neuronal mechanisms of cortical alpha oscillations in awake-behaving macaques. *The Journal of Neuroscience*, *28*(40), 9976–9988. doi:10.1523/JNEUROSCI.2699-08.2008

Buckner, R. L. (2004). Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron*, *44*, 195–208. doi:10.1016/j.neuron.2004.09.006

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences*, *1124*, 1–38. doi:10.1196/annals.1440.011

Busch, N. A., & Herrmann, C. S. (2003). Object-load and feature-load modulate EEG in a short-term memory task. *NeuroReport*, *14*(13), 1721–1724. doi:10.1097/01.wnr.0000087727

Buzsáki, G. (2006). *Rhythms of the Brain* (pp. 1–465). New York: Oxford University Press. doi:10.1093/acprof:oso/9780195301069.001.0001

Buzsáki, G., & Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science*, *304*(5679), 1926–1929. doi:10.1126/science.1099745

Cabeza, R., Ciaramelli, E., & Moscovitch, M. (2012). Cognitive contributions of the ventral parietal cortex: an integrative theoretical account. *Trends in Cognitive Sciences*, *16*(6), 338–352. doi:10.1016/j.tics.2012.04.008

Cabeza, R., Ciaramelli, E., Olson, I. R., & Moscovitch, M. (2008). The parietal cortex and episodic memory: an attentional account. *Nature Reviews. Neuroscience*, *9*(8), 613–625. doi:10.1038/nrn2459

Cabeza, R., & Dennis, N. A. (2013). Frontal lobes and aging: Deterioration and Compensation. In D. T. Stuss & R. T. Knight (Eds.), *Principles of Frontal Lobe Function* (2nd ed., pp. 628–652). New York: Oxford University Press, USA. doi:10.1093/acprof:oso/9780195134971.001.0001

Cabeza, R., & Moscovitch, M. (2013). Memory Systems, Processing Modes, and Components: Functional Neuroimaging Evidence. *Perspectives on Psychological Science*, *8*(1), 49–55. doi:10.1177/1745691612469033

Cabeza, R., & Nyberg, L. (2000). Neural bases of learning and memory: functional neuroimaging evidence. *Current Opinion in Neurology*, *13*(4), 415–421. doi:10.1097/00019052-200008000-00008

Carp, J., Park, J., Polk, T. A., & Park, D. C. (2011). Age differences in neural distinctiveness revealed by multi-voxel pattern analysis. *NeuroImage*, *56*(2), 736–743. doi:10.1016/j.neuroimage.2010.04.267

Catell, R. B. (1966). The scree test for the number of factors. *Multivariate Behavioral Research*, *1*(2), 245–276. doi:10.1207/s15327906mbr0102_10

Chadick, J. Z., & Gazzaley, A. (2011). Differential coupling of visual cortex with default or frontal-parietal network based on goals. *Nature Neuroscience*, *14*(7), 830–832. doi:10.1038/nn.2823

Chen, A., Li, H., Qiu, J., & Luo, Y. (2006). The time course of visual categorization: Electrophysiological evidence from ERP. *Chinese Science Bulletin*, *51*(1), 1–7. doi:10.1007/s11434-006-1586-2

Chen, A., Luo, Y., Wang, Q., Yuan, J., Yao, D., & Li, H. (2007). Electrophysiological correlates of category induction: PSW amplitude as an index of identifying shared attributes. *Biological Psychology*, *76*(3), 230–238. doi:10.1016/j.biopsycho.2007.08.007

Chen, J., Hale, S., & Myerson, J. (2003). Effects of domain, retention interval, and information load on young and older adults' visuospatial working memory. *Aging, Neuropsychology and Cognition*, *10*(2), 122–133. doi:10.1076/anec.10.2.122.14461

Chouinard, P. A., & Paus, T. (2006). The primary motor and premotor areas of the human cerebral cortex. *The Neuroscientist*, *12*(2), 143–152. doi:10.1177/1073858405284255

Christoff, K., & Gabrieli, J. D. E. (2000). The frontopolar cortex and human cognition: Evidence for a rostrocaudal hierarchical organization within the human prefrontal cortex. *Psychobiology*, *28*(2), 168–186. doi:10.3758/BF03331976

Ciaramelli, E., Grady, C. L., & Moscovitch, M. (2008). Top-down and bottom-up attention to memory: a hypothesis (AtoM) on the role of the posterior parietal cortex in memory retrieval. *Neuropsychologia*, *46*(7), 1828–1851. doi:10.1016/j.neuropsychologia.2008.03.022

Clapp, W. C., Rubens, M. T., Sabharwal, J., & Gazzaley, A. (2011). Deficit in switching between functional brain networks underlies the impact of multitasking on working memory in older adults. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(17), 7212–7217. doi:10.1073/pnas.1015297108

Clark, V. P., & Hillyard, S. A. (1996). Spatial Selective Attention Affects Early Extrastriate But Not Striate Components of the Visual Evoked Potential. *Journal of Cognitive Neuroscience*, *8*(5), 387–402. doi:10.1162/jocn.1996.8.5.387

Cohen, J. D., Perlstein, W. M., Braver, T. S., Nystrom, L. E., Noll, D. C., Jonides, J., & Smith, E. E. (1997). Temporal dynamics of brain activation during a working memory task. *Nature*, *386*(6625), 604 –607. doi:10.1038/386604a0

Cohen, M. X. (2011). It's about Time. *Frontiers in Human Neuroscience*, *5*(2). doi:10.3389/fnhum.2011.00002

Cohen, M. X. (2014). *Analyzing Neural Time Series Data: Theory and Practice*. (M. X. Cohen, Ed.) (1st ed., pp. 1–578). MIT Press.

Collignon, O., Girard, S., Gosselin, F., Roy, S., Saint-Amour, D., Lassonde, M., & Lepore, F. (2008). Audio-visual integration of emotion expression. *Brain Research*, *1242*, 126–135. doi:10.1016/j.brainres.2008.04.023

Conway, A. R. A., Jarrold, C., Kane, M. J., Miyake, A., & Towse, J. N. (2007). Variation in Working Memory: An Introduction. In A. R. A. Conway, C. Jarrold, M. J. Kane, A. Miyake, & J. N. Towse (Eds.), *Variation in Working Memory* (pp. 3–18). New York: Oxford University Press.

Cooper, N. R., Croft, R. J., Dominey, S. J. J., Burgess, A. P., & Gruzelier, J. H. (2003). Paradox lost? Exploring the role of alpha oscillations during externally vs. internally directed attention and the implications for idling and inhibition hypotheses. *International Journal of Psychophysiology*, *47*(1), 65–74. doi:10.1016/S0167-8760(02)00107-1

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The reorienting system of the human brain: from environment to theory of mind. *Neuron*, *58*(3), 306–324. doi:10.1016/j.neuron.2008.04.017

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews. Neuroscience*, *3*(3), 201–215. doi:10.1038/nrn755

Cornelissen, F. W., & Greenlee, M. W. (2000). Visual memory for random block patterns defined by luminance and color contrast. *Vision Research*, *40*(3), 287–299. doi:10.1016/S0042-6989(99)00137-6

Cowan, N. (1999). An embedded-processes model of working memory. In A. Miyake & P. Shah (Eds.), *Models of working memory: Mechanisms of active maintenance and executive control.* (1st ed., pp. 62–101). New York: Cambridge University Press. doi:10.1017/S0140525X01003922

Cowan, N. (2008). What are the differences between long-term, short-term, and working memory? *Progress in Brain Research*, *169*(07), 323–338. doi:10.1016/S0079-6123(07)00020-9

Craik, F. I. M., & Byrd, M. (1982). Aging and cognitive deficits: The role of attentional resources. In F. I. M. Craik & S. Trehub (Eds.), *Aging and Cognitive Processes: advances in the study of communication and affect* (pp. 191–211). New York: Plenum Press.

Craik, F. I. M., & Rose, N. S. (2012). Memory encoding and aging: a neurocognitive perspective. *Neuroscience and Biobehavioral Reviews*, *36*(7), 1729–1739. doi:10.1016/j.neubiorev.2011.11.007

Crespo-Garcia, M., Pinal, D., Cantero, J. L., Díaz, F., Zurrón, M., & Atienza, M. (2013). Working Memory Processes Are Mediated by Local and Long-range Synchronization of Alpha Oscillations. *Journal of Cognitive Neuroscience*, *25*(8), 1343–1357. doi:10.1162/jocn_a_00379

Crone, N. E., Sinai, A., & Korzeniewska, A. (2006). High-frequency gamma oscillations and human brain mapping with electrocorticography. *Progress in Brain Research*, *159*(06), 275–295. doi:10.1016/S0079-6123(06)59019-3

D'Esposito, M., Postle, B. R., Ballard, D., & Lease, J. (1999). Maintenance versus manipulation of information held in working memory: an event-related fMRI study. *Brain and Cognition*, *41*(1), 66–86. doi:10.1006/brcg.1999.1096

D'Esposito, M., Postle, B. R., & Rypma, B. (2000). Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. *Experimental Brain Research*, *133*(1), 3–11. doi:10.1007/s002210000395

Dalal, S. S., Sekihara, K., & Nagarajan, S. S. (2006). Modified beamformers for coherent source region suppression. *IEEE Transactions on Biomedical Engineering*, *53*(7), 1357–1363. doi:10.1109/TBME.2006.873752

Danker, J. F., & Anderson, J. R. (2010). The ghosts of brain states past: remembering reactivates the brain regions engaged during encoding. *Psychological Bulletin*, *136*(1), 87–102. doi:10.1037/a0017937

Davidsdottir, S., Cronin-Golomb, A., & Lee, A. (2005). Visual and spatial symptoms in Parkinson's disease. *Vision Research*, *45*(10), 1285–1296. doi:10.1016/j.visres.2004.11.006

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2008). Que PASA? The posterior-anterior shift in aging. *Cerebral Cortex*, *18*(5), 1201–1209. doi:10.1093/cercor/bhm155

Delvenne, J.-F., & Bruyer, R. (2004). Does visual short-term memory store bound features? *Visual Cognition*, *11*(1), 1–27. doi:10.1080/1350628034400016

Di Russo, F., Martinez, A., Sereno, M. I., Pitzalis, S., & Hillyard, S. A. (2001). Cortical sources of the early components of the visual evoked potential. *Human Brain Mapping*, *15*(2), 95–111. doi:10.1002/hbm.10010

Dien, J. (1998). Addressing misallocation of variance in principal components analysis of event-related potentials. *Brain Topography*, *11*(1), 43–55. doi:10.1023/A:1022218503558

Dien, J., Beal, D. J., & Berg, P. (2005). Optimizing principal components analysis of event-related potentials: matrix type, factor loading weighting, extraction, and rotations. *Clinical Neurophysiology*, *116*(8), 1808–1825. doi:10.1016/j.clinph.2004.11.025

Dien, J., & Frishkoff, G. A. (2005). Principal Component Analysis of ERP Data. In T. C. Handy (Ed.), *Event-related potentials a methods handbook* (pp. 189–209). Cambridge, Massachussetts: MIT Press.

Diwakar, M., Huang, M.-X., Srinivasan, R., Harrington, D. L., Robb, A., Angeles, A., … Lee, R. R. (2011). Dual-Core Beamformer for obtaining highly correlated neuronal

networks in MEG. *NeuroImage*, *54*(1), 253–263. doi:10.1016/j.neuroimage.2010.07.023

Donchin, E. (1981). Surprise! ... Surprise? *Psychophysiology*, *18*(5), 493–513. doi:10.1111/j.1469-8986.1981.tb01815.x

Donchin, E., & Coles, M. G. H. (1988). Is the P300 component a manifestation of context updating? *Behavioral and Brain Sciences*, *11*(3), 357–374. doi:10.1017/S0140525X00058027

Donchin, E., & Coles, M. G. H. (1991). While an undergraduate waits. *Neuropsychologia*, *29*(6), 557–569. doi:10.1016/0028-3932(91)90010-6

Eng, H. Y., Chen, D., & Jiang, Y. (2005). Visual working memory for simple and complex visual stimuli. *Psychonomic Bulletin & Review*, *12*(6), 1127–1133. doi:10.3758/BF03206454

Fabiani, M. (2012). It was the best of times, it was the worst of times: a psychophysiologist's view of cognitive aging. *Psychophysiology*, *49*(3), 283–304. doi:10.1111/j.1469-8986.2011.01331.x

Ferrari, V., Bradley, M. M., Codispoti, M., & Lang, P. J. (2010). Detecting novelty and significance. *Journal of Cognitive Neuroscience*, *22*(2), 404–411. doi:10.1162/jocn.2009.21244

Finnigan, S., O'Connell, R. G., Cummins, T. D. R., Broughton, M., & Robertson, I. H. (2011). ERP measures indicate both attention and working memory encoding decrements in aging. *Psychophysiology*, *48*(5), 601–611. doi:10.1111/j.1469-8986.2010.01128.x

Fisher, N. I. (1993). *Statistical Analysis of Circular Data* (Vol. 9, p. 296). Cambridge, U.K.: Cambridge University Press.

Fisher, R. A. (1921). On the" Probable Error" of a Coefficient of Correlation Deduced from a Small Sample. *Metron*, *1*, 3–32.

Fjell, A. M., & Walhovd, K. B. (2001). P300 and neuropsychological tests as measures of aging: scalp topography and cognitive changes. *Brain Topography*, *14*(1), 25–40. doi:10.1023/A:1012563605837

Fletcher, P. C., Frith, C. D., Baker, S. C., Shallice, T., Frackowiak, R. S. J., & Dolan, R. J. (1995). The mind's eye—precuneus activation in memory-related imagery. *Neuroimage*, *2*(3), 195–200. doi:10.1006/nimg.1995.1025

Folstein, J. R., & van Petten, C. (2008). Influence of cognitive control and mismatch on the N2 component of the ERP: a review. *Psychophysiology*, *45*(1), 152–170. doi:10.1111/j.1469-8986.2007.00602.x

Folstein, J. R., & van Petten, C. (2011). After the P3: late executive processes in stimulus categorization. *Psychophysiology*, *48*(6), 825–841. doi:10.1111/j.1469-8986.2010.01146.x

Fort, A., Besle, J., Giard, M.-H., & Pernier, J. (2005). Task-dependent activation latency in human visual extrastriate cortex. *Neuroscience Letters*, *379*(2), 144–148. doi:10.1016/j.neulet.2004.12.076

Fournet, N., Roulin, J.-L., Vallet, F., Beaudoin, M., Agrigoroaei, S., Paignon, A., … Desrichard, O. (2012). Evaluating short-term and working memory in older adults: French normative data. *Aging & Mental Health*, *16*(7), 922–930. doi:10.1080/13607863.2012.674487

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(27), 9673–9678. doi:10.1073/pnas.0504136102

Fransson, P., & Marrelec, G. (2008). The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. *NeuroImage*, *42*(3), 1178–1184. doi:10.1016/j.neuroimage.2008.05.059

Freunberger, R., Klimesch, W., Sauseng, P., Griesmayr, B., Höller, Y., Pecherstorfer, T., & Hanslmayr, S. (2007). Gamma oscillatory activity in a visual discrimination task. *Brain Research Bulletin*, *71*(6), 593–600. doi:10.1016/j.brainresbull.2006.11.014

Freunberger, R., Werkle-Bergner, M., Griesmayr, B., Lindenberger, U., & Klimesch, W. (2011). Brain oscillatory correlates of working memory constraints. *Brain Research*, *1375*, 93–102. doi:10.1016/j.brainres.2010.12.048

Friedman, D. (2012). The components of aging. In S. J. Luck & E. S. Kappenman (Eds.), *Oxford Handbook of event-related potential components* (2012th ed., pp. 513–536). New York: Oxford University Press.

Friedman, D. (2013). The cognitive aging of episodic memory: a view based on the event-related brain potential. *Frontiers in Behavioral Neuroscience*, *7*(111). doi:10.3389/fnbeh.2013.00111

Friedman, D., Nessler, D., & Johnson Jr, R. (2007). Memory encoding and retrieval in the aging brain. *Clinical EEG and Neuroscience*, *38*(1), 2–7. doi:10.1177/155005940703800105

Fries, P., Nikolić, D., & Singer, W. (2007). The gamma cycle. *Trends in Neurosciences*, *30*(7), 309–316. doi:10.1016/j.tins.2007.05.005

Friese, U., Supp, G. G., Hipp, J. F., Engel, A. K., & Gruber, T. (2012). Oscillatory MEG gamma band activity dissociates perceptual and conceptual aspects of visual object processing: a combined repetition/conceptual priming study. *NeuroImage*, *59*(1), 861–871. doi:10.1016/j.neuroimage.2011.07.073

Fuchs, M., Kastner, J., Wagner, M., Hawes, S., & Ebersole, J. S. (2002). A standardized boundary element method volume conductor model. *Clinical Neurophysiology*, *113*(5), 702–712. doi:10.1016/S1388-2457(02)00030-5

Galletti, C., Battaglini, P. P., & Fattori, P. (1991). Functional Properties of Neurons in the Anterior Bank of the Parieto-occipital Sulcus of the Macaque Monkey. *European Journal of Neuroscience*, *3*(5), 452–461. doi:10.1111/j.1460-9568.1991.tb00832.x

Galletti, C., Battaglini, P. P., & Fattori, P. (1995). Eye Position Influence on the Parieto-occipital Area PO (V6) of the Macaque Monkey. *European Journal of Neuroscience*, *7*, 2486–2501. doi:10.1111/j.1460-9568.1995.tb01047.x

García-Larrea, L., & Cézanne-Bert, G. (1998). P3, positive slow wave and working memory load: a study on the functional correlates of slow wave activity. *Electroencephalography and Clinical Neurophysiology*, *108*(3), 260–273. doi:10.1016/S0168-5597(97)00085-3

Gazzaley, A., Clapp, W., Kelley, J., McEvoy, K., Knight, R. T., & D'Esposito, M. (2008). Age-related top-down suppression deficit in the early stages of cortical visual memory processing. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(35), 13122–13126. doi:10.1073/pnas.0806074105

Gazzaley, A., Cooney, J. W., Rissman, J., & D'Esposito, M. (2005). Top-down suppression deficit underlies working memory impairment in normal aging. *Nature Neuroscience*, *8*(10), 1298–1300. doi:10.1038/nn1543

Gazzaley, A., & D'Esposito, M. (2007). Top-down modulation and normal aging. *Annals of the New York Academy of Sciences*, *1097*, 67–83. doi:10.1196/annals.1379.010

Gazzaley, A., Sheridan, M. A., Cooney, J. W., & D'Esposito, M. (2007). Age-related deficits in component processes of working memory. *Neuropsychology*, *21*(5), 532–539. doi:10.1037/0894-4105.21.5.532

Gevins, A., Smith, M. E., McEvoy, L., & Yu, D. (1997). High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of processing, and practice. *Cerebral Cortex*, *7*(4), 374–385. doi:10.1093/cercor/7.4.374

Gilmore, C. S., Clementz, B. A., & Berg, P. (2009). Hemispheric differences in auditory oddball responses during monaural versus binaural stimulation. *International Journal of Psychophysiology*, *73*(3), 326–333. doi:10.1016/j.ijpsycho.2009.05.005

Glisky, E. L. (2007). Changes in cognitive function in human aging. In D. R. Riddle (Ed.), *Brain aging: models, methods, and mechanisms* (pp. 3–20). Boca Ratón (FL): CRC Press. doi:10.1201/9781420005523.sec1

Goh, J. O. S. (2011). Functional Dedifferentiation and Altered Connectivity in Older Adults: Neural Accounts of Cognitive Aging. *Aging and Disease*, *2*(1), 30–48.

Gold, J. M., Murray, R. F., Sekuler, A. B., Bennett, P. J., & Sekuler, R. (2005). Visual memory decay is deterministic. *Psychological Science*, *16*(10), 769–774. doi:10.1111/j.1467-9280.2005.01612.x

Goldberg, I. I., Harel, M., & Malach, R. (2006). When the brain loses its self: prefrontal inactivation during sensorimotor processing. *Neuron*, *50*(2), 329–339. doi:10.1016/j.neuron.2006.03.015

Grady, C. L. (2008). Cognitive neuroscience of aging. *Annals of the New York Academy of Sciences*, *1124*, 127–144. doi:10.1196/annals.1440.009

Grady, C. L. (2012). The cognitive neuroscience of ageing. *Nature Reviews. Neuroscience*, *13*(7), 491–505. doi:10.1038/nrn3256

Grech, R., Cassar, T., Muscat, J., Camilleri, K. P., Fabri, S. G., Zervakis, M., … Vanrumste, B. (2008). Review on solving the inverse problem in EEG source analysis. *Journal of Neuroengineering and Rehabilitation*, *5*(25). doi:10.1186/1743-0003-5-25

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(1), 253–258. doi:10.1073/pnas.0135058100

Griesmayr, B., Gruber, W. R., Klimesch, W., & Sauseng, P. (2010). Human frontal midline theta and its synchronization to gamma during a verbal delayed match to sample task. *Neurobiology of Learning and Memory*, *93*(2), 208–215. doi:10.1016/j.nlm.2009.09.013

Grimault, S., Robitaille, N., Grova, C., Lina, J.-M., Dubarry, A.-S., & Jolicoeur, P. (2009). Oscillatory activity in parietal and dorsolateral prefrontal cortex during retention in visual short-term memory: Additive effects of spatial attention and memory load. *Human Brain Mapping*, *30*(10), 3378–3392. doi:10.1002/hbm.20759

Gundel, A., & Wilson, G. F. (1992). Topographical changes in the ongoing EEG related to the difficulty of mental tasks. *Brain Topography*, *5*(1), 17–25. doi:10.1007/BF01129966

Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nature Reviews. Neuroscience*, *2*(October), 685–694. doi:10.1038/35094500

Haegens, S., Nácher, V., Luna, R., Romo, R., & Jensen, O. (2011). α-Oscillations in the monkey sensorimotor network influence discrimination performance by rhythmical inhibition of neuronal spiking. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(48), 19377–19382. doi:10.1073/pnas.1117190108

Haenschel, C., Bittner, R. A., Waltz, J., Haertling, F., Wibral, M., Singer, W., … Rodriguez, E. (2009). Cortical oscillatory activity is critical for working memory as

revealed by deficits in early-onset schizophrenia. *The Journal of Neuroscience*, *29*(30), 9481–9489. doi:10.1523/JNEUROSCI.1428-09.2009

Hale, S., Rose, N. S., Myerson, J., Strube, M., Sommers, M., Tye-Murray, N., & Spehar, B. (2011). The structure of working memory abilities across the adult life span. *Psychology and Aging*, *26*(1), 92–110. doi:10.1037/a0021483

Halgren, E., Baudena, P., Clarke, J. M., Heit, G., Liégeois, C., Chauvel, P., & Musolino, A. (1995). Intracerebral potentials to rare target and distractor auditory and visual stimuli. I. Superior temporal plane and parietal lobe. *Electroencephalography and Clinical Neurophysiology*, *94*, 191–220. doi:10.1016/0013-4694(94)00259-N

Halgren, E., Squires, N. K., Wilson, C. L., Rohrbaugh, J. W., Babb, T. L., & Crandall, P. H. (1980). Endogenous potentials generated in the human hippocampal formation and amygdala by infrequent events. *Science*, *210*(3), 803–805. doi:10.1126/science.7434000

Hanslmayr, S., & Staudigl, T. (2014). How brain oscillations form memories - A processing based perspective on oscillatory subsequent memory effects. *NeuroImage*, *85*, 648–655. doi:10.1016/j.neuroimage.2013.05.121

Harper, S. (2014). Economic and social implications of aging societies. *Science*, *346*(6209), 587–591. doi:10.1126/science.1254405

Harrison, A., Jolicoeur, P., & Marois, R. (2010). "What" and "where" in the intraparietal sulcus: an FMRI study of object identity and location in visual short-term memory. *Cerebral Cortex*, *20*(10), 2478–2485. doi:10.1093/cercor/bhp314

Harrison, B. J., Pujol, J., López-Solà, M., Hernández-Ribas, R., Deus, J., Ortiz, H., … Cardoner, N. (2008). Consistency and functional specialization in the default mode brain network. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(28), 9781–9786. doi:10.1073/pnas.0711791105

Hartley, A. A., & Speer, N. K. (2000). Locating and fractionating working memory using functional neuroimaging: storage, maintenance, and executive functions. *Microscopy Research and Technique*, *51*(1), 45–53. doi:10.1002/1097-0029(20001001)51:1<45::AID-JEMT5>3.0.CO;2-O

Hasher, L., & Zacks, R. T. (1988). Working Memory, Comprehension, & Aging: A review and new view. *The Psychology of Learning & Motivation*, *22*, 193–225. doi:10.1016/S0079-7421(08)60041-9

Hashtroudi, S., Parker, E. S., Luis, J. D., & Reisen, C. A. (1989). Generation and elaboration in older adults. *Experimental Aging Research*, *15*(2), 73–78. doi:10.1080/03610738908259760

Ho, M.-C., Chou, C.-Y., Huang, C.-F., Lin, Y.-T., Shih, C.-S., Han, S.-Y., … Liu, C.-J. (2012). Age-related changes of task-specific brain activity in normal aging. *Neuroscience Letters*, *507*(1), 78–83. doi:10.1016/j.neulet.2011.11.057

Hoffman, P., Pobric, G., Drakesmith, M., & Lambon Ralph, M. A. (2012). Posterior middle temporal gyrus is involved in verbal and non-verbal semantic cognition: Evidence from rTMS. *Aphasiology*, *26*(9), 1119–1130. doi:10.1080/02687038.2011.608838

Hollingworth, A., Richard, A. M., & Luck, S. J. (2008). Understanding the function of visual short-term memory: transsaccadic memory, object correspondence, and gaze correction. *Journal of Experimental Psychology. General*, *137*(1), 163–181. doi:10.1037/0096-3445.137.1.163

Houlihan, M., Stelmack, R., & Campbell, K. (1998). Intelligence and the effects of perceptual processing demands, task difficulty and processing speed on P300, reaction time and movement time. *Intelligence*, *26*(1), 9–25. doi:10.1016/S0160-2896(99)80049-X

Howard, M. W., Rizzuto, D. S., Caplan, J. B., Madsen, J. R., Lisman, J., Aschenbrenner-Scheibe, R., … Kahana, M. J. (2003). Gamma Oscillations Correlate with Working Memory Load in Humans. *Cerebral Cortex*, *13*(12), 1369–1374. doi:10.1093/cercor/bhg084

Iachini, T., Iavarone, A., Senese, V., Ruotolo, F., & Ruggiero, G. (2009). Visuospatial Memory in Healthy Elderly, AD and MCI: A Review. *Current Aging Science*, *2*(1), 43–59. doi:10.2174/1874609810902010043

Itier, R. J., & Taylor, M. J. (2004). N170 or N1? Spatiotemporal Differences between Object and Face Processing Using ERPs. *Cerebral Cortex*, *14*(2), 132–142. doi:10.1093/cercor/bhg111

Jacques, C., & Rossion, B. (2007). Early electrophysiological responses to multiple face orientations correlate with individual discrimination performance in humans. *NeuroImage*, *36*(3), 863–876. doi:10.1016/j.neuroimage.2007.04.016

James, M. S., Johnstone, S. J., & Hayward, W. G. (2001). Event-Related Potentials, Configural Encoding, and Feature-Based Encoding in Face Recognition. *Journal of Psychophysiology*, *15*(4), 275–285. doi:10.1027//0269-8803.15.4.275

Jensen, O., Bonnefond, M., & VanRullen, R. (2012). An oscillatory mechanism for prioritizing salient unattended stimuli. *Trends in Cognitive Sciences*, *16*(4), 200–206. doi:10.1016/j.tics.2012.03.002

Jensen, O., Gelfand, J., Kounios, J., & Lisman, J. E. (2002). Oscillations in the alpha band (9-12 Hz) increase with memory load during retention in a short-term memory task. *Cerebral Cortex*, *12*(8), 877–882. doi:10.1093/cercor/12.8.877

Jensen, O., Gips, B., Bergmann, T. O., & Bonnefond, M. (2014). Temporal coding organized by coupled alpha and gamma oscillations prioritize visual processing. *Trends in Neurosciences*, *37*(7), 357–369. doi:10.1016/j.tins.2014.04.001

Jensen, O., & Mazaheri, A. (2010). Shaping functional architecture by oscillatory alpha activity: gating by inhibition. *Frontiers in Human Neuroscience*, *4*(186). doi:10.3389/fnhum.2010.00186

John, E. R., Easton, P., Isenhart, R., Allen, P., & Gulyashar, A. (1996). Electrophysiological analysis of the registration, storage and retrieval of information in delayed matching from samples. *International Journal of Psychophysiology*, *24*(1-2), 127–144. doi:10.1016/S0167-8760(96)00056-6

Johnson, J. D., & Rugg, M. D. (2007). Recollection and the reinstatement of encoding-related cortical activity. *Cerebral Cortex*, *17*(11), 2507–2515. doi:10.1093/cercor/bhl156

Johnson Jr, R., & Donchin, E. (1980). P300 and Stimulus Categorization : Two Plus One is not so Different from One Plus One. *Psychophysiology*, *17*(2), 167–178. doi:10.1111/j.1469-8986.1980.tb00131.x

Jokisch, D., & Jensen, O. (2007). Modulation of gamma and alpha activity during a working memory task engaging the dorsal or ventral stream. *The Journal of Neuroscience*, *27*(12), 3244–3251. doi:10.1523/JNEUROSCI.5399-06.2007

Jonides, J., Lewis, R. L., Nee, D. E., Lustig, C. A., Berman, M. G., & Sledge Moore, K. (2008). The mind and brain of short-term memory. *Annual Review of Psychology*, *59*, 193–224. doi:10.1146/annurev.psych.59.103006.093615

Jost, K., Bryck, R. L., Vogel, E. K., & Mayr, U. (2011). Are old adults just like low working memory young adults? Filtering efficiency and age differences in visual working memory. *Cerebral Cortex*, *21*(5), 1147–1154. doi:10.1093/cercor/bhq185

Kaiser, J., Heidegger, T., Wibral, M., Altmann, C. F., & Lutzenberger, W. (2008). Distinct gamma-band components reflect the short-term memory maintenance of different sound lateralization angles. *Cerebral Cortex*, *18*(10), 2286–2295. doi:10.1093/cercor/bhm251

Kalkstein, J., Checksfield, K., Bollinger, J., & Gazzaley, A. (2011). Diminished top-down control underlies a visual imagery deficit in normal aging. *The Journal of Neuroscience*, *31*(44), 15768–15774. doi:10.1523/JNEUROSCI.3209-11.2011

Kane, M. J., & Engle, R. W. (2002). The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: an individual-differences perspective. *Psychonomic Bulletin & Review*, *9*(4), 637–671. doi:10.3758/BF03196323

Kelly, S. P., Lalor, E. C., Reilly, R. B., & Foxe, J. J. (2006). Increases in alpha oscillatory power reflect an active retinotopic mechanism for distracter suppression during sustained visuospatial attention. *Journal of Neurophysiology*, *95*(6), 3844–3851. doi:10.1152/jn.01234.2005

Kennett, S., Eimer, M., Spence, C., & Driver, J. (2001). Tactile-visual links in exogenous spatial attention under different postures: convergent evidence from psychophysics

and ERPs. *Journal of Cognitive Neuroscience*, *13*(4), 1–16. doi:10.1162/08989290152001899

Kent, C., & Lamberts, K. (2008). The encoding-retrieval relationship: retrieval as mental simulation. *Trends in Cognitive Sciences*, *12*(3), 92–98. doi:10.1016/j.tics.2007.12.004

Kessels, R. P. C., Meulenbroek, O., Fernandez, G., & Olde Rikkert, M. G. M. (2010). Spatial working memory in aging and mild cognitive impairment: Effects of task load and contextual cueing. *Aging, Neuropsychology and Cognition*, *17*(5), 556–574. doi:10.1080/13825585.2010.481354

Kessels, R. P. C., Postma, A., Wijnalda, E. M., & de Haan, E. H. F. (2000). Frontal-lobe involvement in spatial memory: evidence from PET, fMRI, and lesion studies. *Neuropsychology Review*, *10*(2), 101–113. doi:10.1023/A:1009016820717

Kitada, R., Okamoto, Y., Sasaki, A. T., Kochiyama, T., Miyahara, M., Lederman, S. J., & Sadato, N. (2013). Early visual experience and the recognition of basic facial expressions: involvement of the middle temporal and inferior frontal gyri during haptic identification by the early blind. *Frontiers in Human Neuroscience*, *7*(7). doi:10.3389/fnhum.2013.00007

Klimesch, W., Fellinger, R., & Freunberger, R. (2011). Alpha oscillations and early stages of visual encoding. *Frontiers in Psychology*, *2*(118). doi:10.3389/fpsyg.2011.00118

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: the inhibition-timing hypothesis. *Brain Research Reviews*, *53*(1), 63–88. doi:10.1016/j.brainresrev.2006.06.003

Klingberg, T. (2006). Development of a superior frontal-intraparietal network for visuo-spatial working memory. *Neuropsychologia*, *44*(11), 2171–2177. doi:10.1016/j.neuropsychologia.2005.11.019

Knott, V., Millar, A., Dulude, L., Bradford, L., Alwahhabi, F., Lau, T., … Wiens, A. (2004). Event-related potentials in young and elderly adults during a visual spatial working memory task. *Clinical EEG and Neuroscience*, *35*(4), 185–192.

Kok, A. (1997). Event-related-potential (ERP) reflections of mental resources: a review and synthesis. *Biological Psychology*, *45*(1-3), 19–56. doi:10.1016/S0301-0511(96)05221-0

Kok, A. (2001). On the utility of P3 amplitude as a measure of processing capacity. *Psychophysiology*, *38*(3), 557–577. doi:10.1017/S0048577201990559

Kooij, D., de Lange, A., Jansen, P., & Dikkers, J. (2008). Older workers' motivation to continue to work: five meanings of age: A conceptual review. *Journal of Managerial Psychology*, *23*(4), 364–394. doi:10.1108/02683940810869015

Kramer, A., Schneider, W., Fisk, A., & Donchin, E. (1986). The Effects of Practice and Task Structure on Components of the Event-Related Brain Potential. *Psychophysiology*, *23*(1), 33–48. doi:10.1111/j.1469-8986.1986.tb00590.x

Krause, C. M., Sillanmäki, L., Koivisto, M., Saarela, C., Häggqvist, A., Laine, M., & Hämäläinen, H. (2000). The effects of memory load on event-related EEG desynchronization and synchronization. *Clinical Neurophysiology*, *111*(11), 2071–2078. doi:10.1016/S1388-2457(00)00429-6

Kutas, M., McCarthy, G., & Donchin, E. (1977). Augmenting mental chronometry: The P300 as a measure of stimulus evaluation time. *Science*, *197*(4305), 792–795. doi:10.1126/science.887923

Lacadie, C. M., Fulbright, R. K., Rajeevan, N., Constable, R. T., & Papademetris, X. (2008). More accurate Talairach coordinates for neuroimaging using non-linear registration. *NeuroImage*, *42*(2), 717–725. doi:10.1016/j.neuroimage.2008.04.240

Lachaux, J. P., Rodriguez, E., Martinerie, J., & Varela, F. J. (1999). Measuring phase synchrony in brain signals. *Human Brain Mapping*, *8*(4), 194–208. doi:10.1002/(SICI)1097-0193(1999)8:4<194::AID-HBM4>3.0.CO;2-C

Lehmann, D., Ozaki, H., & Pal, I. (1987). EEG alpha map series: brain micro-states by space-oriented adaptive segmentation. *Electroencephalography and Clinical Neurophysiology*, *67*(3), 271–288. doi:10.1016/0013-4694(87)90025-3

Leiberg, S., Lutzenberger, W., & Kaiser, J. (2006). Effects of memory load on cortical oscillatory activity during auditory pattern working memory. *Brain Research*, *1120*(1), 131–140. doi:10.1016/j.brainres.2006.08.066

Linden, D. E. J. (2007). The working memory networks of the human brain. *The Neuroscientist*, *13*(3), 257–267. doi:10.1177/1073858406298480

Lindín, M., Zurrón, M., & Díaz, F. (2004). Changes in P300 amplitude during an active standard auditory oddball task. *Biological Psychology*, *66*(2), 153–167. doi:10.1016/j.biopsycho.2003.10.007

Lorenzo-López, L., Amenedo, E., Pascual-Marqui, R. D., & Cadaveira, F. (2008). Neural correlates of age-related visual search decline: a combined ERP and sLORETA study. *NeuroImage*, *41*(2), 511–524. doi:10.1016/j.neuroimage.2008.02.041

Luck, S. J. (2005). *An Introduction to Event-Related Potentials and Their Neural Origins*. *An introduction to event related potentials technique*. Cambridge, London: MIT Press.

Luck, S. J. (2012). Event-related Potentials. In H. Cooper, P. M. Camic, D. L. Long, A. T. Panter, D. Rindskopf, & K. J. Sher (Eds.), *APA handbook of research methods in psychology: Foundations, planning, measures and psychometrics* (1st ed., Vol. 1, pp. 523–546). Washington, DC: American Psychological Association. doi:10.1037/13619-028

Luck, S. J., Heinze, H. J., Mangun, G. R., & Hillyard, S. A. (1990). Visual event-related potentials index focused attention within bilateral stimulus arrays. II. Functional dissociation of P1 and N1 components. *Electroencephalography and Clinical Neurophysiology*, *75*(6), 528–542. doi:10.1016/00134694(90)90139-B

Luck, S. J., & Hillyard, S. A. (1994). Electrophysiological correlates of feature analysis during visual search. *Psychophysiology*, *31*(3), 291–308. doi:10.1111/j.1469-8986.1994.tb02218.x

Luck, S. J., & Vogel, E. K. (1997). The capacity of visual working memory for features and conjunctions. *Nature*, *390*(6657), 279–281. doi:10.1038/36846

Lustig, C., Snyder, A. Z., Bhakta, M., O'Brien, K. C., McAvoy, M., Raichle, M. E., … Buckner, R. L. (2003). Functional deactivations: change with age and dementia of the Alzheimer type. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(24), 14504–14509. doi:10.1073/pnas.2235925100

Magliero, A., Bashore, T. R., Coles, M. G. H., & Donchin, E. (1984). On the dependence of P300 latency on stimulus evaluation processes. *Psychophysiology*, *21*(2), 171–186. doi:10.1111/j.1469-8986.1984.tb00201.x

Manelis, A., Hanson, C., & Hanson, S. J. (2011). Implicit memory for object locations depends on reactivation of encoding-related brain regions. *Human Brain Mapping*, *32*(1), 32–50. doi:10.1002/hbm.20992

Margulies, D. S., Vincent, J. L., Kelly, C., Lohmann, G., Uddin, L. Q., Biswal, B. B., … Petrides, M. (2009). Precuneus shares intrinsic functional architecture in humans and monkeys. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(47), 20069–20074. doi:10.1073/pnas.0905314106

Mason, M. F., Norton, M. I., van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering minds: the default network and stimulus-independent thought. *Science*, *315*(5810), 393–395. doi:10.1126/science.1131295

Mazziotta, J., Toga, A., Evans, A., Fox, P., Lancaster, J., Zilles, K., … Mazoyer, B. (2001). A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *356*(1412), 1293–1322. doi:10.1098/rstb.2001.0915

McCarthy, G., Wood, C. C., Williamson, P. D., & Spencer, D. D. (1989). Task-dependent field potentials in human hippocampal formation. *The Journal of Neuroscience*, *9*(12), 4253–4268.

McEvoy, L. K., Pellouchoud, E., Smith, M. E., & Gevins, A. (2001). Neurophysiological signals of working memory in normal aging. *Cognitive Brain Research*, *11*(3), 363–376. doi:10.1016/S0926-6410(01)00009-X

McEvoy, L. K., Smith, M. E., & Gevins, A. (1998). Dynamic cortical networks of verbal and spatial working memory: effects of memory load and task practice. *Cerebral Cortex*, *8*(7), 563–574. doi:10.1093/cercor/8.7.563

Mecklinger, A., & Ullsperger, P. (1993). P3 varies with stimulus categorization rather than probability. *Electroencephalography and Clinical Neurophysiology*, *86*(6), 395–407. doi:10.1016/0013-4694(93)90135-I

Mecklinger, A., & Ullsperger, P. (1995). The P300 to novel and target events: a spatio-temporal dipole model analysis. *Neuroreport*, *7*(1), 241–245.

Meltzer, J. A., Zaveri, H. P., Goncharova, I. I., Distasio, M. M., Papademetris, X., Spencer, S. S., … Constable, R. T. (2008). Effects of working memory load on oscillatory power in human intracranial EEG. *Cerebral Cortex*, *18*(8), 1843–1855. doi:10.1093/cercor/bhm213

Michels, L., Bucher, K., Lüchinger, R., Klaver, P., Martin, E., Jeanmonod, D., & Brandeis, D. (2010). Simultaneous EEG-fMRI during a working memory task: modulations in low and high frequency bands. *PLoS ONE*, *5*(4), e10298. doi:10.1371/journal.pone.0010298

Michels, L., Moazami-Goudarzi, M., Jeanmonod, D., & Sarnthein, J. (2008). EEG alpha distinguishes between cuneal and precuneal activation in working memory. *NeuroImage*, *40*(3), 1296–1310. doi:10.1016/j.neuroimage.2007.12.048

Miller, E. K., Erickson, C. A., & Desimone, R. (1996). Neural mechanisms of visual working memory in prefrontal cortex of the macaque. *The Journal of Neuroscience*, *16*(16), 5154–5167.

Missonnier, P., Gold, G., Leonards, U., Costa-Fazio, L., Michel, J.-P., Ibáñez, V., & Giannakopoulos, P. (2004). Aging and working memory: early deficits in EEG activation of posterior cortical areas. *Journal of Neural Transmission*, *111*(9), 1141–1154. doi:10.1007/s00702-004-0159-2

Missonnier, P., Herrmann, F. R., Rodriguez, C., Deiber, M.-P., Millet, P., Fazio-costa, L., … Giannakopoulos, P. (2011). Age-related differences on event-related potentials and brain rhythm oscillations during working memory activation. *Journal of Neural Transmission*, *118*(6), 945–955. doi:10.1007/s00702-011-0600-2

Mo, J., Schroeder, C. E., & Ding, M. (2011). Attentional modulation of alpha oscillations in macaque inferotemporal cortex. *The Journal of Neuroscience*, *31*(3), 878–882. doi:10.1523/JNEUROSCI.5295-10.2011

Moore, T., & Armstrong, K. M. (2003). Selective gating of visual signals by microstimulation of frontal cortex. *Nature*, *421*(6921), 370–373. doi:10.1038/nature01285

Morgan, H. M., Klein, C., Boehm, S. G., Shapiro, K. L., & Linden, D. E. J. (2008). Working memory load for faces modulates P300, N170, and N250r. *Journal of Cognitive Neuroscience*, *20*(6), 989–1002. doi:10.1162/jocn.2008.20072

Müller, N. G., & Knight, R. T. (2002). Age-related changes in fronto-parietal networks during spatial memory: an ERP study. *Cognitive Brain Research*, *13*(2), 221–234. doi:10.1016/S0926-6410(01)00119-7

Müller, N. G., & Knight, R. T. (2006). The functional neuroanatomy of working memory: contributions of human brain lesion studies. *Neuroscience*, *139*(1), 51–58. doi:10.1016/j.neuroscience.2005.09.018

Näätänen, R., & Picton, T. (1987). The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. *Psychophysiology*, *24*(4), 375–425. doi:10.1111/j.1469-8986.1987.tb00311.x

Nasman, V. T., & Rosenfeld, J. P. (1990). Parietal P3 response as an indicator of stimulus categorization: increased P3 amplitude to categorically deviant target and nontarget stimuli. *Psychophysiology*, *27*(3), 338–350. doi:10.1111/j.1469-8986.1990.tb00393.x

Newman, S. D., Just, M. A., & Carpenter, P. A. (2002). The synchronization of the human cortical working memory network. *NeuroImage*, *15*(4), 810–822. doi:10.1006/nimg.2001.0997

Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Human Brain Mapping*, *15*(1), 1–25. doi:10.1002/hbm.1058

Nittono, H., Shibuya, Y., & Hori, T. (2007). Anterior N2 predicts subsequent viewing time and interest rating for novel drawings. *Psychophysiology*, *44*(5), 687–696. doi:10.1111/j.1469-8986.2007.00539.x

Noack, H., Lövdén, M., & Lindenberger, U. (2012). Normal aging increases discriminal dispersion in visuospatial short-term memory. *Psychology and Aging*, *27*(3), 627–637. doi:10.1037/a0027251

Nunez, P. L., Srinivasan, R., Westdorp, A. F., Wijesinghe, R. S., Tucker, D. M., Silberstein, R. B., & Cadusch, P. J. (1997). EEG coherency: I: statistics, reference electrode, volume conduction, Laplacians, cortical imaging, and interpretation at multiple scales. *Electroencephalography and Clinical Neurophysiology*, *103*, 499–515. doi:10.1016/S0013-4694(97)00066-7

Nyberg, L., Habib, R., McIntosh, A. R., & Tulving, E. (2000). Reactivation of encoding-related brain activity during memory retrieval. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(20), 11120–11124. doi:10.1073/pnas.97.20.11120

O'Connell, R. G., Balsters, J. H., Kilcullen, S. M., Campbell, W., Bokde, A. W., Lai, R., … Robertson, I. H. (2012). A simultaneous ERP/fMRI investigation of the P300 aging effect. *Neurobiology of Aging*, *33*(10), 2448–2461. doi:10.1016/j.neurobiolaging.2011.12.021

Oberauer, K., & Kliegl, R. (2001). Beyond resources: Formal models of complexity effects and age differences in working memory. *European Journal of Cognitive Psychology*, *13*(1-2), 187–215. doi:10.1080/09541440042000278

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, *9*(1), 97–113. doi:10.1016/0028-3932(71)90067-4

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J.-M. (2011). FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational Intelligence and Neuroscience*, *2011*, 156869. doi:10.1155/2011/156869

Oostenveld, R., Praamstra, P., Stegeman, D. F., & van Oosterom, A. (2001). Overlap of attention and movement-related activity in lateralized event-related brain potentials. *Clinical Neurophysiology*, *112*(3), 477–484. doi:10.1016/S1388-2457(01)00460-6

Osipova, D., Hermes, D., & Jensen, O. (2008). Gamma power is phase-locked to posterior alpha activity. *PLoS ONE*, *3*(12), e3990. doi:10.1371/journal.pone.0003990

Owen, A. M. (1997). The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging. *European Journal of Neuroscience*, *9*(7), 1329–1339. doi:10.1111/j.1460-9568.1997.tb01487.x

Palva, J. M., Monto, S., Kulashekhar, S., & Palva, S. (2010). Neuronal synchrony reveals working memory networks and predicts individual memory capacity. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(16), 7580–7585. doi:10.1073/pnas.0913113107

Palva, S., Kulashekhar, S., Hämäläinen, M. S., & Palva, J. M. (2011). Localization of cortical phase and amplitude dynamics during visual working memory encoding and retention. *The Journal of Neuroscience*, *31*(13), 5013–5025. doi:10.1523/JNEUROSCI.5592-10.2011

Palva, S., & Palva, J. M. (2007). New vistas for alpha-frequency band oscillations. *Trends in Neurosciences*, *30*(4), 150–158. doi:10.1016/j.tins.2007.02.001

Palva, S., & Palva, J. M. (2011). Functional roles of alpha-band phase synchronization in local and large-scale cortical networks. *Frontiers in Psychology*, *2*, Article 204. doi:10.3389/fpsyg.2011.00204

Park, D. C. (2000). The basic mechanism, accounting for age-related decline in cognitive function. In D. C. Park & N. Schwarz (Eds.), *Cognitive aging: A primer* (pp. 3–21). Philadelphia (PA): Psychology Press.

Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N. S., Smith, A. D., & Smith, P. K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychology and Aging*, *17*(2), 299–320. doi:10.1037//0882-7974.17.2.299

Park, D. C., Polk, T. A., Hebrank, A. C., & Jenkins, L. J. (2010). Age differences in default mode activity on easy and difficult spatial judgment tasks. *Frontiers in Human Neuroscience*, *3*(75). doi:10.3389/neuro.09.075.2009

Park, D. C., Polk, T. A., Mikels, J. A., Taylor, S. F., & Marshuetz, C. (2001). Cerebral aging: integration of brain and behavioral models of cognitive function. *Dialogues in Clinical Neuroscience*, *3*(3), 151–165.

Park, D. C., & Reuter-Lorenz, P. A. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annual Review of Psychology*, *60*, 21.1–21.24. doi:10.1146/annurev.psych.59.103006.093656

Pascual-Marqui, R. D. (1999). Review of methods for solving the EEG inverse problem. *International Journal of Bioelectromagnetism*, *1*(1), 75–86.

Pascual-Marqui, R. D. (2002). Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. *Methods & Fndings in Experimental & Clinical Pharmacology*, *24 Suppl D*, 5–12.

Pascual-Marqui, R. D., Michel, C. M., & Lehmann, D. (1994). Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. *International Journal of Psychophysiology*, *18*(1), 49–65. doi:10.1016/0167-8760(84)90014-X

Passaro, A. D., Elmore, L. C., Ellmore, T. M., Leising, K. J., Papanicolaou, A. C., & Wright, A. A. (2013). Explorations of object and location memory using fMRI. *Frontiers in Behavioral Neuroscience*, *7*, Article 105. doi:10.3389/fnbeh.2013.00105

Paxton, J. L., Barch, D. M., Racine, C. A., & Braver, T. S. (2008). Cognitive control, goal maintenance, and prefrontal function in healthy aging. *Cerebral Cortex*, *18*(5), 1010–1028. doi:10.1093/cercor/bhm135

Paynter, C. A., Reder, L. M., & Kieffaber, P. D. (2009). Knowing we know before we know: ERP correlates of initial feeling-of-knowing. *Neuropsychologia*, *47*(3), 796–803. doi:10.1016/j.neuropsychologia.2008.12.009

Peich, M.-C., Husain, M., & Bays, P. M. (2013). Age-related decline of precision and binding in visual working memory. *Psychology and Aging*, *28*(3), 729–743. doi:10.1037/a0033236

Pelosi, L., & Blumhardt, L. D. (1999). Effects of age on working memory: an event-related potential study. *Cognitive Brain Research*, *7*(3), 321–334. doi:10.1016/S0926-6410(98)00035-4

Percival, D. B., & Walden, A. T. (1993). *Spectral Analysis for Physical Applications: Multitaper and Conventional Univariate Techniques* (Vol. 38, p. 583). Cambridge, U.K.: Cambridge University Press. doi:10.1017/CBO9780511622762

Persson, J., Lustig, C., Nelson, J. K., & Reuter-Lorenz, P. A. (2007). Age differences in deactivation: a link to cognitive control? *Journal of Cognitive Neuroscience*, *19*(6), 1021–1032. doi:10.1162/jocn.2007.19.6.1021

Petrides, M. (2000). The role of the mid-dorsolateral prefrontal cortex in working memory. *Experimental Brain Research*, *133*(1), 44–54. doi:10.1007/s002210000399

Pfurtscheller, G., Stancák, A., & Neuper, C. (1996). Event-related synchronization (ERS) in the alpha band--an electrophysiological correlate of cortical idling: a review. *International Journal of Psychophysiology*, *24*(1-2), 39–46. doi:10.1016/S0167-8760(96)00066-9

Phillips, W. A. (1974). On the distinction between sensory storage and short-term visual memory. *Perception & Psychophysics*, *16*(2), 283–290. doi:10.3758/BF03203943

Phillips, W. A., & Baddeley, A. D. (1971). Reaction time and short-term visual memory. *Psychonomic Science*, *22*(2), 73–74. doi:10.3758/BF03332500

Picton, T. W., Bentin, S., Berg, P., Donchin, E., Hillyard, S. A., Johnson Jr, R., … Taylor, M. J. (2000). Guidelines for using human event-related potentials to study cognition: recording standards and publication criteria. *Psychophysiology*, *37*(2), 127–152. doi:10.1017/S0048577200000305

Pinal, D., Zurrón, M., & Díaz, F. (2014). Effects of load and maintenance duration on the time course of information encoding and retrieval in working memory: from perceptual analysis to post-categorization processes. *Frontiers in Human Neuroscience*, *8*(165). doi:10.3389/fnhum.2014.00165

Polich, J. (1996). Meta-analysis of P300 normative aging studies. *Psychophysiology*, *33*(4), 334–353. doi:10.1111/j.1469-8986.1996.tb01058.x

Polich, J. (2003). Theoretical overview of P3a and P3b. In J. Polich (Ed.), *Detection of Change: Event-related potential and fMRI findings* (pp. 83–98). Boston: Springer US. doi:10.1007/978-1-4615-0294-4_5

Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. *Clinical Neurophysiology*, *118*(10), 2128–2148. doi:10.1016/j.clinph.2007.04.019

Posada, A., Hugues, E., Franck, N., Vianin, P., & Kilner, J. (2003). Augmentation of induced visual gamma activity by increased task complexity. *European Journal of Neuroscience*, *18*(8), 2351–2356. doi:10.1046/j.1460-9568.2003.02962.x

Posner, R. A. (1995). *Aging and old age* (p. 375). Chicago: The University of Chicago Press.

Postle, B. R., & D'Esposito, M. (1999). What-Then-Where in visual working memory: an event-related fMRI study. *Journal of Cognitive Neuroscience*, *11*(6), 585–597. doi:10.1162/089892999563652

Postle, B. R., Druzgal, T. J., & D'Esposito, M. (2003). Seeking the neural substrates of visual working memory storage. *Cortex*, *3*(4-5), 927–946. doi:10.1016/S0010-9452(08)70871-2

Potts, G. F. (2004). An ERP index of task relevance evaluation of visual stimuli. *Brain and Cognition*, *56*(1), 5–13. doi:10.1016/j.bandc.2004.03.006

Potts, G. F., & Tucker, D. M. (2001). Frontal evaluation and posterior representation in target detection. *Cognitive Brain Research*, *11*(1), 147–156. doi:10.1016/S0926-6410(00)00075-6

Pratt, H., Michalewski, H. J., Patterson, J. V, & Starr, A. (1989). Brain potentials in a memory-scanning task. II. Effects of aging on potentials to the probes. *Electroencephalography and Clinical Neurophysiology*, *72*(6), 507–517. doi:10.1016/0013-4694(89)90228-9

Pritchard, W. S., Shappell, S. A., & Brandt, M. E. (1991). Psychophysiology of N200/N400: a review and classification scheme. In J. R. Jennings, P. K. Ackles, & M. G. H. Coles (Eds.), *Advances in psychophysiology: A research annual (Vol. 4)* (Vol. 4, pp. 43–106). London: Jessica Kingsley.

Raffone, A., & Wolters, G. (2001). A cortical mechanism for binding in visual working memory. *Journal of Cognitive Neuroscience*, *13*(6), 766–785. doi:10.1162/08989290152541430

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(2), 676–682. doi:10.1073/pnas.98.2.676

Raichle, M. E., & Snyder, A. Z. (2007). A default mode of brain function: a brief history of an evolving idea. *NeuroImage*, *37*(4), 1083–1090. doi:10.1016/j.neuroimage.2007.02.041

Rajagovindan, R., & Ding, M. (2011). From prestimulus alpha oscillation to visual-evoked response: an inverted-U function and its attentional modulation. *Journal of Cognitive Neuroscience*, *23*(6), 1379–1394. doi:10.1162/jocn.2010.21478

Ramnani, N., & Owen, A. M. (2004). Anterior prefrontal cortex: insights into function from anatomy and neuroimaging. *Nature Reviews. Neuroscience*, *5*(3), 184–194. doi:10.1038/nrn1343

Ranganath, C. (2006). Working memory for visual objects: complementary roles of inferior temporal, medial temporal, and prefrontal cortex. *Neuroscience*, *139*(1), 277–289. doi:10.1016/j.neuroscience.2005.06.092

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., … Acker, J. D. (2005). Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cerebral Cortex*, *15*(11), 1676–1689. doi:10.1093/cercor/bhi044

Reuter-Lorenz, P. A., & Cappell, K. A. (2008). Neurocognitive aging and the compensation hypothesis. *Current Directions in Psychological Science*, *17*(3), 177–182. doi:10.1111/j.1467-8721.2008.00570.x

Reuter-Lorenz, P. A., & Park, D. C. (2010). Human neuroscience and the aging mind: a new look at old problems. *Journal of Gerontology: Psychological Sciences*, *65B*(4), 405–415. doi:10.1093/geronb/gbq035

Reuter-Lorenz, P. A., Stanczak, L., & Miller, A. C. (1999). Neural Recruitment and Cognitive Aging: Two Hemispheres Are Better Than One, Especially as You Age. *Psychological Science*, *10*(6), 494–500. doi:10.1111/1467-9280.00195

Roland, P. E., Gulyas, B., Seitz, R. J., Bohm, C., & Stone-Elander, S. (1990). Functional anatomy of storage, recall, and recognition of a visual pattern in man. *NeuroReport*, *1*(1), 53–56.

Rönnlund, M., Nyberg, L., Bäckman, L., & Nilsson, L.-G. (2005). Stability, growth, and decline in adult life span development of declarative memory: cross-sectional and longitudinal data from a population-based study. *Psychology and Aging*, *20*(1), 3–18. doi:10.1037/0882-7974.20.1.3

Rossini, P. M., Del Percio, C., Pasqualetti, P., Cassetta, E., Binetti, G., Dal Forno, G., … Babiloni, C. (2006). Conversion from mild cognitive impairment to Alzheimer's disease is predicted by sources and coherence of brain electroencephalography rhythms. *Neuroscience*, *143*(3), 793–803. doi:10.1016/j.neuroscience.2006.08.049

Rousselet, G. A., Gaspar, C. M., Pernet, C. R., Husk, J. S., Bennett, P. J., & Sekuler, A. B. (2010). Healthy aging delays scalp EEG sensitivity to noise in a face discrimination task. *Frontiers in Psychology*, *1*(19). doi:10.3389/fpsyg.2010.00019

Rousselet, G. A., Husk, J. S., Pernet, C. R., Gaspar, C. M., Bennett, P. J., & Sekuler, A. B. (2009). Age-related delay in information accrual for faces: evidence from a parametric, single-trial EEG approach. *BMC Neuroscience*, *10*(114). doi:10.1186/1471-2202-10-114

Roux, F., & Uhlhaas, P. J. (2014). Working memory and neural oscillations: alpha–gamma versus theta–gamma codes for distinct WM information? *Trends in Cognitive Sciences*, *18*(1), 16–25. doi:10.1016/j.tics.2013.10.010

Rugg, M. D., Johnson, J. D., Park, H., & Uncapher, M. R. (2008). Encoding-retrieval overlap in human episodic memory: a functional neuroimaging perspective. *Progress in Brain Research*, *169*, 339–352. doi:10.1016/S0079-6123(07)00021-0

Rugg, M. D., & Morcom, A. M. (2005). The relationship between brain activity, cognitive performance and aging: the case of memory. In R. Cabeza, L. Nyberg, & D. C. Park (Eds.), *Cognitive neuroscience of aging: Linking cognitive and cerebral aging.* (pp. 132–156). New York: Oxford University Press.

Sadaghiani, S., Scheeringa, R., Lehongre, K., Morillon, B., Giraud, A.-L., & Kleinschmidt, A. (2010). Intrinsic connectivity networks, alpha oscillations, and tonic alertness: a

simultaneous electroencephalography/functional magnetic resonance imaging study. *The Journal of Neuroscience*, *30*(30), 10243–10250. doi:10.1523/JNEUROSCI.1004-10.2010

Sadato, N., Yonekura, Y., Waki, A., Yamada, H., & Ishii, Y. (1997). Role of the supplementary motor area and the right premotor cortex in the coordination of bimanual finger movements. *The Journal of Neuroscience*, *17*(24), 9667–9674.

Saliasi, E., Geerligs, L., Lorist, M. M., & Maurits, N. M. (2013). The Relationship between P3 Amplitude and Working Memory Performance Differs in Young and Older Adults. *PLoS ONE*, *8*(5), e63701. doi:10.1371/journal.pone.0063701

Salthouse, T. A. (1990). Working memory as a processing resource in cognitive aging. *Developmental Review*, *10*(1), 101–124. doi:10.1016/0273-2297(90)90006-P

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, *103*(3), 403–428. doi:10.1037/0033-295X.103.3.403

Salthouse, T. A. (2000). Aging and measures of processing speed. *Biological Psychology*, *54*(1-3), 35–54. doi:10.1016/S0301-0511(00)00052-1

Sambataro, F., Murty, V. P., Callicott, J. H., Tan, H.-Y., Das, S., Weinberger, D. R., & Mattay, V. S. (2010). Age-related alterations in default mode network: impact on working memory performance. *Neurobiology of Aging*, *31*(5), 839–852. doi:10.1016/j.neurobiolaging.2008.05.022

Sander, M. C., Lindenberger, U., & Werkle-Bergner, M. (2012). Lifespan age differences in working memory: a two-component framework. *Neuroscience and Biobehavioral Reviews*, *36*(9), 2007–2033. doi:10.1016/j.neubiorev.2012.06.004

Sander, M. C., Werkle-Bergner, M., & Lindenberger, U. (2011). Contralateral delay activity reveals life-span age differences in top-down modulation of working memory contents. *Cerebral Cortex*, *21*(12), 2809–2819. doi:10.1093/cercor/bhr076

Sander, M. C., Werkle-Bergner, M., & Lindenberger, U. (2012). Amplitude modulations and inter-trial phase stability of alpha-oscillations differentially reflect working memory constraints across the lifespan. *NeuroImage*, *59*(1), 646–654. doi:10.1016/j.neuroimage.2011.06.092

Sauseng, P., Feldheim, J. F., Freunberger, R., & Hummel, F. C. (2011). Right Prefrontal TMS Disrupts Interregional Anticipatory EEG Alpha Activity during Shifting of Visuospatial Attention. *Frontiers in Psychology*, *2*, Article 241. doi:10.3389/fpsyg.2011.00241

Sauseng, P., Griesmayr, B., Freunberger, R., & Klimesch, W. (2010). Control mechanisms in working memory: a possible function of EEG theta oscillations. *Neuroscience and Biobehavioral Reviews*, *34*(7), 1015–1022. doi:10.1016/j.neubiorev.2009.12.006

Sauseng, P., & Klimesch, W. (2008). What does phase information of oscillatory brain activity tell us about cognitive processes? *Neuroscience and Biobehavioral Reviews*, *32*(5), 1001–1013. doi:10.1016/j.neubiorev.2008.03.014

Sauseng, P., Klimesch, W., Doppelmayr, M., Pecherstorfer, T., Freunberger, R., & Hanslmayr, S. (2005). EEG alpha synchronization and functional coupling during top-down processing in a working memory task. *Human Brain Mapping*, *26*(2), 148–155. doi:10.1002/hbm.20150

Sauseng, P., Klimesch, W., Heise, K. F., Gruber, W. R., Holz, E., Karim, A. A., … Hummel, F. C. (2009). Brain Oscillatory Substrates of Visual Short-Term Memory Capacity. *Current Biology*, *19*(21), 1846–1852. doi:10.1016/j.cub.2009.08.062

Sauseng, P., Klimesch, W., Schabus, M., & Doppelmayr, M. (2005). Fronto-parietal EEG coherence in theta and upper alpha reflect central executive functions of working memory. *International Journal of Psychophysiology*, *57*(2), 97–103. doi:10.1016/j.ijpsycho.2005.03.018

Sauseng, P., Klimesch, W., Stadler, W., Schabus, M., Doppelmayr, M., Hanslmayr, S., … Birbaumer, N. (2005). A shift of visual spatial attention is selectively associated with human EEG alpha activity. *European Journal of Neuroscience*, *22*(11), 2917–2926. doi:10.1111/j.1460-9568.2005.04482.x

Schack, B., & Klimesch, W. (2002). Frequency characteristics of evoked and oscillatory electroencephalic activity in a human memory scanning task. *Neuroscience Letters*, *331*(2), 107–110. doi:10.1016/S0304-3940(02)00846-7

Schack, B., Weiss, S., & Rappelsberger, P. (2003). Cerebral information transfer during word processing: where and when does it occur and how fast is it? *Human Brain Mapping*, *19*(1), 18–36. doi:10.1002/hbm.10104

Schapkin, S. A., Gusev, A. N., & Kuhl, J. (2000). Categorization of unilaterally presented emotional words: an ERP analysis. *Acta Neurobiologiae Experimentalis*, *60*(1), 17–28.

Scheeringa, R., Petersson, K. M., Oostenveld, R., Norris, D. G., Hagoort, P., & Bastiaansen, M. C. M. (2009). Trial-by-trial coupling between EEG and BOLD identifies networks related to alpha and theta EEG power increases during working memory maintenance. *NeuroImage*, *44*(3), 1224–1238. doi:10.1016/j.neuroimage.2008.08.041

Schendan, H. E., & Lucia, L. C. (2010). Object-sensitive activity reflects earlier perceptual and later cognitive processing of visual objects between 95 and 500 ms. *Brain Research*, *1329*, 124–141. doi:10.1016/j.brainres.2010.01.062

Schmitt, B. M., Münte, T. F., & Kutas, M. (2000). Electrophysiological estimates of the time course of semantic and phonological encoding during implicit picture naming. *Psychophysiology*, *37*(4), 473–484. doi:10.1017/S0048577200981782

Schmitt, B. M., Rodriguez-Fornells, A., Kutas, M., & Münte, T. F. (2001). Electrophysiological estimates of semantic and syntactic information access during tacit picture naming and listening to words. *Neuroscience Research*, *41*(3), 293–298. doi:10.1016/S0168-0102(01)00286-3

Schmitt, B. M., Schiltz, K., Zaake, W., Kutas, M., & Münte, T. F. (2001). An electrophysiological analysis of the time course of conceptual and syntactic encoding during tacit picture naming. *Journal of Cognitive Neuroscience*, *13*(4), 510–522. doi:10.1162/08989290152001925

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., … Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of Neuroscience*, *27*(9), 2349–2356. doi:10.1523/JNEUROSCI.5587-06.2007

Shah, P., & Miyake, A. (1999). Models of working memory. An Introduction. In A. Miyake & P. Shah (Eds.), *Models of working memory: Mechanisms of active maintenance and executive control* (1st ed., pp. 1–27). New York: Cambridge University Press.

Shibasaki, H., & Hallett, M. (2006). What is the Bereitschaftspotential? *Clinical Neurophysiology*, *117*(11), 2341–2356. doi:10.1016/j.clinph.2006.04.025

Singer, W. (2009). Distributed processing and temporal codes in neuronal networks. *Cognitive Neurodynamics*, *3*(3), 189–196. doi:10.1007/s11571-009-9087-z

Smith, E. E., & Jonides, J. (1999). Storage and Executive Processes in the Frontal Lobes. *Science*, *283*(5408), 1657–1661. doi:10.1126/science.283.5408.1657

Soltani, M., & Knight, R. T. (2000). Neural origins of the P300. *Critical Reviews in Neurobiology*, *14*(3&4), 199–224. doi:10.1615/CritRevNeurobiol.v14.i3-4.20

Soria Bauser, D. A., Mayer, K., Daum, I., & Suchan, B. (2011). Encoding/retrieval dissociation in working memory for human body forms. *Behavioural Brain Research*, *220*(1), 65–73. doi:10.1016/j.bbr.2011.01.032

Spaak, E., Bonnefond, M., Maier, A., Leopold, D. A., & Jensen, O. (2012). Layer-specific entrainment of gamma-band neural activity by the alpha rhythm in monkey visual cortex. *Current Biology*, *22*(24), 2313–2318. doi:10.1016/j.cub.2012.10.020

Spreng, R. N., & Grady, C. L. (2010). Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. *Journal of Cognitive Neuroscience*, *22*(6), 1112–1123. doi:10.1162/jocn.2009.21282

Spreng, R. N., Mar, R. A., & Kim, A. S. N. (2009). The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. *Journal of Cognitive Neuroscience*, *21*(3), 489–510. doi:10.1162/jocn.2008.21029

Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(34), 12569–12574. doi:10.1073/pnas.0800005105

Stam, C. J., Nolte, G., & Daffertshofer, A. (2007). Phase lag index: assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. *Human Brain Mapping*, *28*(11), 1178–1193. doi:10.1002/hbm.20346

Sternberg, S. (1966). High-speed scanning in human memory. *Science*, *153*(3736), 652–654. doi:10.1126/science.153.3736.652

Stipacek, A., Grabner, R. H., Neuper, C., Fink, A., & Neubauer, A. C. (2003). Sensitivity of human EEG alpha band desynchronization to different working memory components and increasing levels of memory load. *Neuroscience Letters*, *353*(3), 193–196. doi:10.1016/j.neulet.2003.09.044

Strik, W. K., Fallgatter, A. J., Brandeis, D., & Pascual-Marqui, R. D. (1998). Three-dimensional tomography of event-related potentials during response inhibition: evidence for phasic frontal lobe activation. *Electroencephalography and Clinical Neurophysiology*, *108*(4), 406–413. doi:10.1016/S0168-5597(98)00021-5

Studer, P., Wangler, S., Diruf, M. S., Kratz, O., Moll, G. H., & Heinrich, H. (2010). ERP effects of methylphenidate and working memory load in healthy adults during a serial visual working memory task. *Neuroscience Letters*, *482*(2), 172–176. doi:10.1016/j.neulet.2010.07.030

Sullivan, E. V, & Pfefferbaum, A. (2006). Diffusion tensor imaging and aging. *Neuroscience and Biobehavioral Reviews*, *30*(6), 749–761. doi:10.1016/j.neubiorev.2006.06.002

Sutton, S., Tueting, P., Zubin, J., & John, E. R. (1967). Information delivery and the sensory evoked potential. *Science*, *155*(3768), 1436–1439. doi:10.1126/science.155.3768.1436

Talairach, J., & Tournoux, P. (1988). *Co-Planar Stereotaxis Atlas of the Human Brain. 3-D Proportional System: An Approach to Cerebral Imaging* (1st ed., Vol. 270, p. 132). New York: Thieme.

Tallon-Baudry, C., & Bertrand, O. (1999). Oscillatory gamma activity in humans and its role in object representation. *Trends in Cognitive Sciences*, *3*(4), 151–162. doi:10.1016/S1364-6613(99)01299-1

Tallon-Baudry, C., Kreiter, A., & Bertrand, O. (1999). Sustained and transient oscillatory responses in the gamma and beta bands in a visual short-term memory task in humans. *Visual Neuroscience*, *16*(3), 449–459. doi:10.1017/S0952523899163065

Taylor, M. J. (2002). Non-spatial attentional effects on P1. *Clinical Neurophysiology*, *113*(12), 1903–1908. doi:10.1016/S1388-2457(02)00309-7

Thut, G., Nietzel, A., Brandt, S. A., & Pascual-Leone, A. (2006). Alpha-band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *The Journal of Neuroscience*, *26*(37), 9494–9502. doi:10.1523/JNEUROSCI.0875-06.2006

Todd, J. J., & Marois, R. (2004). Capacity limit of visual short-term memory in human posterior parietal cortex. *Nature*, *428*(6984), 751–754. doi:10.1038/nature02466

Töllner, T., Gramann, K., Müller, H. J., & Eimer, M. (2009). The anterior N1 component as an index of modality shifting. *Journal of Cognitive Neuroscience*, *21*(9), 1653–1669. doi:10.1162/jocn.2009.21108

Tomasi, D., Ernst, T., Caparelli, E. C., & Chang, L. (2006). Common deactivation patterns during working memory and visual attention tasks: an intra-subject fMRI study at 4 Tesla. *Human Brain Mapping*, *27*(8), 694–705. doi:10.1002/hbm.20211

Townsend, J. T., & Ashby, F. G. (1978). Methods of Modeling Capacity in Simple Processing Systems. In N. J. Castellan & F. Restle (Eds.), *Cognitive theory (Volume 3)* (pp. 199–239). Hillsdale, New Jersey: Lawrence Erlbaum Associates Ltd.

Tuladhar, A. M., ter Huurne, N., Schoffelen, J.-M., Maris, E., Oostenveld, R., & Jensen, O. (2007). Parieto-occipital sources account for the increase in alpha activity with working memory load. *Human Brain Mapping*, *28*(8), 785–792. doi:10.1002/hbm.20306

Ungerleider, L. G., & Haxby, J. V. (1994). "What" and "where" in the human brain. *Current Opinion in Neurobiology*, *4*(2), 157–165. doi:10.1016/0959-4388(94)90066-3

Vallesi, A., Stuss, D. T., McIntosh, A. R., & Picton, T. W. (2009). Age-related differences in processing irrelevant information: evidence from event-related potentials. *Neuropsychologia*, *47*(2), 577–586. doi:10.1016/j.neuropsychologia.2008.10.018

Van der Ham, I. J. M., van Strien, J. W., Oleksiak, A., van Wezel, R. J. A., & Postma, A. (2010). Temporal characteristics of working memory for spatial relations: An ERP study. *International Journal of Psychophysiology*, *77*(2), 83–94. doi:10.1016/j.ijpsycho.2010.04.008

Van der Ham, I. J. M., van Wezel, R. J. A., Oleksiak, A., & Postma, A. (2007). The time course of hemispheric differences in categorical and coordinate spatial processing. *Neuropsychologia*, *45*(11), 2492–2498. doi:10.1016/j.neuropsychologia.2007.03.021

Van der Meij, R., Kahana, M., & Maris, E. (2012). Phase-amplitude coupling in human electrocorticography is spatially distributed and phase diverse. *The Journal of Neuroscience*, *32*(1), 111–123. doi:10.1523/JNEUROSCI.4816-11.2012

Van Elk, M., van Schie, H. T., Neggers, S. F. W., & Bekkering, H. (2010). Neural and temporal dynamics underlying visual selection for action. *Journal of Neurophysiology*, *104*(2), 972–983. doi:10.1152/jn.01079.2009

Van Vugt, M. K., Chakravarthi, R., & Lachaux, J.-P. (2014). For whom the bell tolls: periodic reactivation of sensory cortex in the gamma band as a substrate of visual working memory maintenance. *Frontiers in Human Neuroscience*, *8*, Article 696. doi:10.3389/fnhum.2014.00696

Vanni, S., Revonsuo, A., & Hari, R. (1997). Modulation of the Parieto-Occipital Alpha Rhythm during Object Detection. *The Journal of Neuroscience*, *17*(18), 7141–7147.

Varela, F., Lachaux, J.-P., Rodriguez, E., & Martinerie, J. (2001). The brainweb: phase synchronization and large-scale integration. *Nature Reviews. Neuroscience*, *2*(April), 229–239. doi:10.1038/35067550

Vaughan JR, H. G., Costa, L. D., & Ritter, W. (1968). Topography of the human motor potential. *Electroencephalography and Clinical Neurophysiology*, *25*(1), 1–10. doi:10.1016/0013-4694(68)90080-1

Verleger, R. (1997). On the utility of P3 latency as an index of mental chronometry. *Psychophysiology*, *34*, 131–156. doi:10.1111/j.1469-8986.1997.tb02125.x

Verleger, R., Heide, W., Butt, C., & Kömpf, D. (1994). Reduction of P3b in patients with temporo-parietal lesions. *Cognitive Brain Research*, *2*, 103–116. doi:10.1016/0926-6410(94)90007-8

Vogel, E. K., & Luck, S. J. (2000). The visual N1 component as an index of a discrimination process. *Psychophysiology*, *37*(2), 190–203. doi:10.1111/1469-8986.3720190

Vogel, E. K., Woodman, G. F., & Luck, S. J. (2001). Storage of features, conjunctions, and objects in visual working memory. *Journal of Experimental Psychology: Human Perception and Performance*, *27*(1), 92–114. doi:10.1037/0096-1523.27.1.92

Von Stein, A., & Sarnthein, J. (2000). Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization. *International Journal of Psychophysiology*, *38*(3), 301–313. doi:10.1016/S0167-8760(00)00172-0

Wang, Y., Song, Y., Qu, Z., & Ding, Y. (2010). Task difficulty modulates electrophysiological correlates of perceptual learning. *International Journal of Psychophysiology*, *75*(3), 234–240. doi:10.1016/j.ijpsycho.2009.11.006

Wechsler, D. (1997). Wechsler Adult Intelligence Scale—Third edition. San Antonio, Texas.: The Psychological Corporation.

Werkle-Bergner, M., Müller, V., Li, S.-C., & Lindenberger, U. (2006). Cortical EEG correlates of successful memory encoding: implications for lifespan comparisons. *Neuroscience and Biobehavioral Reviews*, *30*(6), 839–854. doi:10.1016/j.neubiorev.2006.06.009

West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychological Bulletin*, *120*(2), 272–292. doi:10.1037/0033-2909.120.2.272

Wijers, A. A., Mulder, G., Okita, T., & Mulder, L. J. M. (1989). Event-Related Potentials During Memory Search and Selective Attention to Letter Size and Conjunctions of Letter Size and Color. *Psychophysiology*, *26*(5), 529–547. doi:10.1111/j.1469-8986.1989.tb00706.x

Wimber, M., Maaß, A., Staudigl, T., Richardson-Klavehn, A., & Hanslmayr, S. (2012). Rapid memory reactivation revealed by oscillatory entrainment. *Current Biology*, *22*, 1482–1486. doi:10.1016/j.cub.2012.05.054

Womelsdorf, T., & Fries, P. (2007). The role of neuronal synchronization in selective attention. *Current Opinion in Neurobiology*, *17*(2), 154–160. doi:10.1016/j.conb.2007.02.002

Worden, M. S., Foxe, J. J., Wang, N., & Simpson, G. V. (2000). Anticipatory biasing of visuospatial attention indexed by retinotopically specific alpha-band electroencephalography increases over occipital cortex. *The Journal of Neuroscience*, *20*(6), RC63.

Xu, Y., & Chun, M. M. (2006). Dissociable neural mechanisms supporting visual short-term memory for objects. *Nature*, *440*(7080), 91–95. doi:10.1038/nature04262

Yamagishi, N., Callan, D. E., Goda, N., Anderson, S. J., Yoshida, Y., & Kawato, M. (2003). Attentional modulation of oscillatory activity in human visual cortex. *NeuroImage*, *20*(1), 98–113. doi:10.1016/S1053-8119(03)00341-0

Yamazaki, T., Kamijo, K.-I., Kenmochi, A., Fukuzumi, S., Kiyuna, T., Takaki, Y., & Kuroiwa, Y. (2000). Multiple equivalent current dipole source localization of visual event-related potentials during oddball paradigm with motor response. *Brain Topography*, *12*(3), 159–175. doi:10.1023/A:1023467806268

Yamazaki, T., Kamijo, K.-I., Kiyuna, T., Takaki, Y., & Kuroiwa, Y. (2001). Multiple dipole analysis of visual event-related potentials during oddball paradigm with silent counting. *Brain Topography*, *13*(3), 161–168. doi:10.1023/A:1007851018184

Yanagisawa, T., Yamashita, O., Hirata, M., Kishima, H., Saitoh, Y., Goto, T., … Kamitani, Y. (2012). Regulation of motor representation by phase-amplitude coupling in the sensorimotor cortex. *The Journal of Neuroscience*, *32*(44), 15467–15475. doi:10.1523/JNEUROSCI.2929-12.2012

Yao, J., & Dewald, J. P. A. (2005). Evaluation of different cortical source localization methods using simulated and experimental EEG data. *NeuroImage*, *25*(2), 369–382. doi:10.1016/j.neuroimage.2004.11.036

Yin, J., Gao, Z., Jin, X., Ye, L., Shen, M., & Shui, R. (2011). Tracking the mismatch information in visual short term memory: an event-related potential study. *Neuroscience Letters*, *491*(1), 26–30. doi:10.1016/j.neulet.2011.01.001

Yingling, C. D., & Hosobuchi, Y. (1984). A subcortical correlate of P300 in man. *Electroencephalography and Clinical Neurophysiology*, *59*, 72–76. doi:10.1016/0168-5597(84)90022-4

Zanto, T. P., Toy, B., & Gazzaley, A. (2010). Delays in neural processing during working memory encoding in normal aging. *Neuropsychologia*, *48*(1), 13–25. doi:10.1016/j.neuropsychologia.2009.08.003

Zeki, S. (1990). A Century of Cerebral Achromatopsia. *Brain*, *113*(6), 1721–1777. doi:10.1093/brain/113.6.1721

Zhang, W., & Luck, S. J. (2008). Discrete fixed-resolution representations in visual working memory. *Nature*, *453*(7192), 233–235. doi:10.1038/nature06860

Zhang, Y., & Ding, M. (2010). Detection of a weak somatosensory stimulus: Role of the prestimulus mu rhythm and its top–down modulation. *Journal of Cognitive Neuroscience*, *22*(2), 307–322. doi:10.1162/jocn.2009.21247

Zimmer, H. D. (2008). Visual and spatial working memory: from boxes to networks. *Neuroscience and Biobehavioral Reviews*, *32*(8), 1373–1395. doi:10.1016/j.neubiorev.2008.05.016

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

Appendix

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

RESUMO

A poboación mundial está a envellecer. Xa que logo, aumentan o número e proporción de persoas con máis de 64 anos, e ó mesmo tempo as ratios de dependencia desta poboación. Estes aumentos débense ás melloras en saúde e estilos de vida dos últimos séculos, porén o avellentamento segue a implicar unha serie de cambios perniciosos, especialmente con respecto ás capacidades cognitivas (Arking, 2006; Posner, 1995). Amais, este avellentamento cognitivo afecta en especial á memoria de traballo (MT) viso-espacial (Park et al., 2002), a cal serve de base a outros procesos cognitivos superiores e a gran parte das actividades da vida diaria (Baddeley, 2003). Así é que, tendo como obxectivo fomentar melloras na calidade de vida e independencia dos maiores, é necesario afondar no coñecemento sobre os aspectos básicos e a evolución ó longo do ciclo vital da MT viso-espacial.

A MT viso-espacial pode definirse como a capacidade para manter e/ou manipular durante breves períodos de tempo (i.e. uns poucos segundos) pequenas cantidades de información viso-espacial que xa non están dispoñibles no entorno (Cowan, 1999). Dita capacidade é usualmente dividida en tres eventos cognitivos: a codificación, o mantemento e a recuperación de información (Jonides et al., 2008). Para o estudo da actividade cerebral subxacente a estes eventos cognitivos de forma independente uns doutros, é necesario empregar tarefas de emparellamento demorado; xa que estas tarefas constan de tres etapas diferenciadas que se corresponden con cada un destes eventos (John, Easton, Isenhart, Allen, & Gulyashar, 1996). Amais, nestas tarefas pódese manipular de forma sinxela a carga en memoria e a duración do período de mantemento, que son dous factores que limitan a capacidade da MT.

Neste senso, a aproximación tradicional ó estudo da MT viso-espacial dende as neurociencias perseguía a localización de procesos mentais en diferentes rexións corticais (Cohen, 2014). Se ben esta tradición aportou datos valiosos en canto ás bases neuro-anatómicas da MT, os aspectos relacionados coa estrutura temporal da actividade cerebral son aínda imprecisos. Xa que logo, o estudo do sinal electroencefalográfico (e.g. a través dos potenciais evocados (PE) ou da análise da actividade oscilatoria) en tarefas de emparellamento demorado pode ser de grande utilidade, xa que permite ós investigadores capturar as rápidas, dinámicas e secuencias operacións neurais que constitúen a codificación, mantemento e recuperación de información, así como estudar os efectos que sobre estas operacións teñen a carga en memoria e a duración do período de mantemento. Máis aínda, este tipo de estudos poderían arroxar luz sobre o impacto que os procesos de avellentamento normal teñen sobre a actividade eléctrica cerebral subxacente á MT viso-espacial.

O estudo sobre diferentes aspectos da codificación e a recuperación de información viso-espacial en MT feito ata agora con PE ten posto de manifesto a relación dos

compoñentes P1 e N1 con procesos perceptivos (Luck, Heinze, Mangun, & Hillyard, 1990), así como a relación de P2 (Potts, 2004) e N2 (Folstein & van Petten, 2008) con diferentes aspectos da avaliación do estímulo. O compoñente P300, o cal relacionase coa categorización de estímulos (Johnson Jr & Donchin, 1980; Kok, 2001), tamén foi observado neste tipo de estudos. Con todo, non coñecemos estudos previos que integrasen estes diferentes compoñentes para determinar a estrutura temporal destes eventos cognitivos. Ademais, estudos previos teñen amosado resultados contrapostos en relación ós efectos da carga en memoria sobre as latencias e amplitudes destes compoñentes tanto durante a codificación como durante a recuperación (e.g. Morgan, Klein, Boehm, Shapiro, & Linden, 2008; Soria Bauser, Mayer, Daum, & Suchan, 2011). Os efectos da duración do período de mantemento, pola súa parte, só foron investigados no compoñente N2 dos potencias evocados durante a recuperación de información (van der Ham, van Strien, Oleksiak, van Wezel, & Postma, 2010).

En canto a actividade eléctrica cerebral durante o mantemento de información, diferentes bandas de frecuencia foron relacionadas con diferentes aspectos deste evento cognitivo. Así, mentres a actividade beta (12-30 Hz) e gamma (>30 Hz) asociouse ó mantemento de representacións da información (Tallon-Baudry, Kreiter, & Bertrand, 1999), a actividade theta (4-6 Hz) e alfa (8-12 Hz) asociáronse a procesos de control executivo (Sauseng et al., 2009). Deste xeito, a sincronía entre a fase de alfa e a amplitude de beta e gamma é considerada un mecanismo para o control do fluxo de información en pequenos circuítos corticais, no que alfa actúa ofrecendo ventas de excitación e inhibición do procesamento neural nas que se aniña a actividade beta e gamma (Jensen & Mazaheri, 2010). Así e todo, existe controversia no xeito en que a carga en memoria modula a actividade alfa, posto que tanto incrementos (e.g. Schack & Klimesch, 2002) coma diminucións (e.g. Gundel & Wilson, 1992) na súa amplitude foron observados en estudos previos. Non obstante, resultados de estudos recentes en primates non humanos observaron fontes de actividade alfa en diferentes rexións das vías de procesamento visual (Bollimunta, Chen, Schroeder, & Ding, 2008; Mo, Schroeder, & Ding, 2011), o que abre a posibilidade a que diferentes dinámicas de alfa podan coexistir nun mesmo momento en diferentes rexións corticais, sen que este extremo se demostrase en humanos.

Finalmente, existen diferentes teorías para explicar o deterioro da execución en tarefas de memoria observado en adultos maiores en comparación con mozos. De esta forma, suxeriuse que hai unha diminución xeneralizada na velocidade de procesamento neural asociada ós procesos de envellecemento (Salthouse, 1996). Tamén se suxeriu que os maiores teñen unha capacidade reducida da MT con respecto ós mozos, o que pode ser debido a unha redución nos recursos de procesamento dispoñibles (Craik & Byrd, 1982) ou a un déficit nos procesos inhibitorios (Hasher & Zacks, 1988).

A hipótese dunha diminución na velocidade de procesamento ten sido apoiada por resultados condutuais e por resultados de investigacións con PE, as cales observaron

maiores latencias en compoñentes coma N1 e P300 tanto durante a codificación (Zanto, Toy, & Gazzaley, 2010) como durante a recuperación (Müller & Knight, 2002). Pola contra, non se ten examinado a posible redución na cantidade de recursos dispoñibles para o procesamento de estímulos viso-espaciais complexos durante eses eventos cognitivos. Amais, a pesares de que se observou un déficit na inhibición da actividade dunha serie de rexións corticais cuxa actividade é característica de estados de repouso (Sambataro et al., 2010), non se examinou o rol da sincronización da actividade oscilatoria destas diferentes rexións nesta ineficiente coordinación da actividade das redes funcionais relevantes e irrelevantes para a tarefa.

En consecuencia, para o presente traballo de doutoramento realizáronse cinco estudos experimentais que tentaron dar resposta ós seguintes obxectivos:

I- Determinar o curso temporal da actividade eléctrica cerebral durante a codificación e a recuperación de información, mediante o exame dos PE (**Estudo 1**).

II.- Investigar a modulación pola carga en memoria e a duración do período de mantemento nos compoñentes dos PE identificados para a codificación e recuperación de información en memoria (**Estudo 1**).

III.- Examinar a actividade oscilatoria durante o mantemento de información en memoria e a súa modulación pola carga en memoria, con particular interese en estudar se diferentes dinámicas da actividade alfa poden coexistir en diferentes rexións corticais neste período (**Estudo 2**).

IV.- Analizar os efectos do avellentamento e a súa interacción cos da MT e a duración do período de mantemento sobre os compoñentes dos PE identificados para a codificación (**Estudo 3**) e recuperación (**Estudo 4**) de información. E, deste xeito, examinar as evidencias en favor das hipóteses sobre unha diminución da velocidade do procesamento e dunha redución dos recursos de procesamento asociadas á idade.

V.- Explorar as diferenzas entre mozos e maiores na actividade oscilatoria durante o mantemento de información en memoria, centrándose nos mecanismos inter-rexionais de acoplamento da fase de alfa e a amplitude de gamma polo seu posible papel na coordinación da actividade en redes funcionais de longa distancia (**Estudo 5**).

Para estes cinco estudos deseñouse unha tarefa de emparellamento demorado na que os participantes debían memorizar o número e posición dos puntos dunha ficha de dominó presentada durante 1000 ms (codificación). Logo, despois dun período de 2500 ou 5000 ms libre de estimulación no que os participantes debían manter a información recén memorizada (período de mantemento), os participantes tiñan un máximo de 3000 ms para escoller entre tres alternativas a ficha de dominó que foxe idéntica á que memorizaron e premer o correspondente botón nun aparello de resposta (recuperación/recoñecemento). Amais, manipulouse a posición e número de puntos nas fichas para xerar dúas condicións de carga en memoria, e se aproveitaron as dúas extensións de tempo diferentes entre a

codificación e a recuperación para xerar dúas condicións de duración do período de mantemento. Esta tarefa, ademais. foi adaptada para o rexistro da actividade electroencefalográfica. Polo que tanto a execución condutual como o sinal EEG foron analizados.

Así, no **Estudo 1**, empregouse unha análise de compoñentes principais (Dien, 1998) para determinar de forma obxectiva os diferentes elos que conforman o curso temporal da actividade eléctrica cerebral durante a codificación e a recuperación. Os resultados desta análise revelaron que a actividade de ambos eventos cognitivos segue un curso temporal moi similar, composto por seis compoñentes que pola súa latencia dende a presentación do estímulo e a súa distribución no coiro cabeludo correspondíanse cos seguintes compoñentes dos PE: P1, N1, P2, N2, P300 e unha onda lenta positiva na codificación e negativa durante a recuperación.

En este mesmo estudo, a comparación entre as dúas condicións de carga en memoria amosou que en alta carga a execución era menos precisa e máis lenta que en baixa carga. Así mesmo, a amplitude de P300 foi menor na condición de alta que na de baixa carga en memoria durante a codificación e a recuperación. En troques, a amplitude da onda lenta foi maior na condición de alta que na de baixa carga en memoria durante a codificación, en tanto que a de N2 foino durante a recuperación. Así pois, parece que a carga en memoria reduce os recursos de procesamento para a categorización do estímulo ó seren captados por procesos de elaboración e mantemento da información durante a codificación e por procesos de clasificación do estímulo durante a recuperación. Tamén unha maior carga en memoria asociouse a unha redución da actividade en rexións frontais asociadas ó estado de repouso (e.g. frontal medial e partes do córtex cingulado anterior (véxase Raichle et al., 2001)) en diferentes momentos da codificación e recuperación de información. Así como a un aumento da actividade en áreas que teñen sido relacionadas con procesos de coordinación da atención prestada a representacións mentais e a estímulos externos (i.e. xiro frontal medio correspondente á área 10 de Brodmann (véxase Christoff & Gabrieli, 2000)) durante a recuperación e coincidindo coa latencia de N2.

Ademais, a pesares de que a duración do período de mantemento non afectou á execución na tarefa, unha duración longa do período de mantemento asociouse a maior amplitude de N2 e a maior actividade no córtex temporal superior esquerdo que os observados para duración curtas. Non obstante, a latencia de P300 era menor nesta última condición que na de duración longa do período de mantemento. Por tanto, serán necesarios máis traballos no futuro para clarificar os efectos deste factor sobre a execución e a actividade eléctrica cerebral en tarefas de MT.

Os resultados do **Estudo 2**, que examinou a actividade eléctrica durante o mantemento de información, mostraron que esta caracterizouse por un incremento da potencia de alfa en rexións corticais posteriores e irrelevantes para a tarefa con respecto a un período de liña base. Estas áreas parieto-occipitais foron localizadas nas proximidades do suco

parieto-occipital. Así pois, isto parece apoiar o rol inhibitorio da actividade alfa para controlar o fluxo de información durante o mantemento de información, de xeito que se inhibe o procesamento de materiais sensorio-motores irrelevantes para evitar interferencias no procesamento de informacións relevantes.

Amais, este incremento na potencia de alfa con respecto á liña base era concorrente a unha redución dependente da carga na potencia de alfa en áreas frontais do hemisferio esquerdo e parietais bilaterais, as cales forman parte da rede funcional relevante para a tarefa. Así mesmo, a carga en memoria tamén se relacionou cunha diminución na sincronía da fase de alfa entre as áreas frontais e parietais, na que a fase de alfa nas áreas frontais precedía á das áreas parietais. Estes trocos asociados a unha maior carga en memoria parecen indicar unha redución da inhibición en áreas relevantes para a tarefa levada a cabo por mecanismos de control executivo "arriba-abaixo", a cal coexiste co aumento de inhibición nas áreas irrelevantes para a tarefa.

No **Estudo 3**, os resultados das análises dos datos condutuais revelaron unha execución da tarefa máis pobre nos adultos maiores que nos mozos, así coma unha peor execución na condición de alta que na de baixa carga en memoria unicamente no grupo de adultos maiores. Xa que logo, estes resultados confirman a sensibilidade da tarefa de emparellamento demorado ó declive da MT viso-espacial asociado á idade e están en liña coas predicións das hipóteses sobre a diminución na velocidade de procesamento e sobre a redución da capacidade da MT coa idade.

Polo que respecta ás latencias e amplitudes dos compoñentes dos PE durante a codificación de información en memoria, encontrouse que as latencias de P2 e N2 foron máis longas nos maiores que nos mozos. Ademais, a latencia de N2 relacionábase directamente coa precisión nas respostas á tarefa cando se controlaron os efectos da idade cronolóxica, se ben o efecto era significativo tan só no grupo de maiores cando as correlacións foron calculadas para cada grupo por separado. Deste xeito, parece existir unha diminución da velocidade de procesamento asociada á idade que afecta de maneira específica ós procesos de análise e avaliación do estímulo, a tenor das maiores latencias de P2 e N2 (respectivamente). Máis aínda, parece que os adultos maiores necesitan máis tempo para realizar unha avaliación satisfactoria do estímulo durante a súa codificación en memoria, o que lles permitiría manter un alto nivel na execución da tarefa.

Por outra banda, os adultos maiores, tamén, presentaban menores amplitudes que os mozos nos compoñentes P2 e P300. Isto, podería apuntar á existencia dunha diminución asociada á idade na mobilización ou na cantidade de recursos de procesamento dispoñibles para a avaliación e categorización dos estímulos. Se ben, cabe salientar que non se observou ningunha interacción entre os efectos da idade e os efectos da carga en memoria, polo que parece que os PE dos adultos maiores e dos mozos durante a codificación de información son modulas dunha forma similar pola carga en memoria.

Con respecto ó **Estudo 4**, nel se compararon entre ambos grupos de idade e entre as dúas condición de carga en memoria e as dúas de duración do período de mantemento as latencias e amplitudes dos PE durante a recuperación de información en MT. A comparación das latencias entre os dous grupos de idade revelou maiores latencias para N2 e P300 en adultos maiores que en mozos. Xa que logo, é de forma similar ó observado durante a codificación de información, a evidencia apunta que a diminución da velocidade de procesamento asociada á idade centrase na avaliación e, neste caso, a categorización dos estímulos. Estes aspectos téñense asociado ós compoñentes N2 e P300, respectivamente.

No que se refire ás amplitudes, non se observaron diferenzas significativas entre os dous grupos de idade. Porén, si se atoparon interaccións entre os efectos da idade e os efectos da duración do período de mantemento e da carga en memoria. De modo que, por unha banda, a amplitude de N1 foi maior despois de períodos longos que de períodos curtos só nos mozos. Isto indica que os mozos modularon o procesamento perceptivo en función da duración do período de mantemento, en tanto que os adultos maiores non mostraron tal diferenza.

Por outra banda, a amplitude de P300 foi maior en eléctrodos parietais que frontais na condición de baixa carga só nos mozos. En consecuencia, os mozos mostraron unha distribución máis uniforme da amplitude de P300 na condición de alta carga que na de baixa carga. O cal podería indicar que para afrontar as maiores demandas cognitivas da condición de alta carga os mozos teñen unha maior dependencia dos recursos frontais con respecto os parietais. Pola súa parte, os adultos maiores mostran esta distribución máis homoxénea da amplitude de P300 en ambas condicións de carga en memoria. Así pois, parece ser que os adultos maiores teñen maior dependencia dos recursos frontais con respecto os parietais, o cal está en liña coa hipótese dun desprazamento do recrutamento de recursos de áreas posteriores a áreas anteriores coa idade (PASA, polas súas siglas en inglés (véxase Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008)). Esta hipótese xerouse na investigación dos procesos de recoñecemento na memoria episódica a longo prazo, e polo tanto, os resultados do presente estudo estenderían os seus postulados ós mecanismos de recoñecemento de información en MT. Asemade, este resultado podería indicar que os adultos maiores mostran signos de esforzo cognitivo similares ós dos mozos inda que a menores niveis de demanda cognitiva, o que apoiaría os postulados da hipótese do andamiaxe neurocognitivo (véxase Park & Reuter-Lorenz, 2009).

Finalmente, o **Estudo 5**, examinou os efectos da idade na actividade oscilatoria durante o mantemento de información en memoria e a súa modulación pola carga en memoria. Ademais, púxose especial énfase en examinar se a relación da fase de alfa frontal coa amplitude de beta e gamma en rexións posteriores podería ser un mecanismo neural subxacente á coordinación de redes funcionais de longa distancia. E dado o rol inhibitorio da actividade alfa, tamén se avaliou se este mecanismo sofre alteracións coa idade que

podan explicar porque os adultos maiores mostran maior actividade na rede irrelevante que na relevante para a tarefa durante o mantemento de información en memoria.

A comparación da actividade oscilatoria entre os dous grupos de idade revelou maiores amplitudes da actividade beta de rexión temporais do hemisferio esquerdo en maiores que en mozos. Esta actividade, ademais, correlacionou co tempo de reacción, polo que estes resultados poderían indicar que xoves e maiores empregaron diferentes estratexias para o mantemento de información viso-espacial en MT, e que a estratexia dos maiores foi menos eficiente que a dos mozos.

En canto ás diferenzas da actividade oscilatoria entre as dúas condicións de carga en memoria, ambos grupos mostraron un aumento da actividade alfa en rexións frontais, que pese a ser máis disperso nos maiores, solapábase no córtex cingulado anterior. Esta rexión forma parte da "salience network", que ten como función a coordinación da actividade entre as redes relevante e irrelevante para a tarefa. Xa que logo, este resultado parece indicar que a maior carga foi necesario maior esforzo para coordinar ambas redes funcionais.

Así pois, a análise da relación da fase de alfa nesta rexión coa amplitude de beta e gamma en rexións posteriores revelou un acoplamento significativo entre a fase de alfa e a actividade gamma en áreas relevantes para a tarefa (i.e. xiros angular e supramarxinal) e en áreas irrelevantes (i.e. precuneus). Así a todo, dito acoplamento sucedía en diferentes ángulos da fase de alfa para os dous tipos de áreas e para os dous grupos. Isto é, os mozos amosaban a actividade gamma de rexións relevantes para a tarefa na fase excitadora de alfa, e os maiores na fase inhibidora. Pola contra, os mozos presentaban a actividade das rexións irrelevantes durante a fase inhibidora de alfa frontal, en tanto que os adultos maiores facíano durante a fase excitadora de alfa en rexións frontais. Xa que logo, os resultados parecen indicar que o acoplamento entre a fase de alfa en rexións frontais e a actividade gamma en rexións posteriores é un mecanismo neural encargado da coordinación de redes corticais de longa distancia. Deste xeito, os adultos maiores parecen presentar unha falla de sincronía entre os diferentes nodos da rede relevante para a tarefa, en tanto que manteñen sincronizadas rexións da rede de repouso.

Amais, esta falta de desconexión na redes irrelevante semella estar detrás do declive na memoria a curto prazo relacionado coa idade, posto que observouse unha relación significativa entre a fase de alfa na que se acoplaba a actividade gamma de áreas irrelevantes e os tempos de reacción e as taxas de acerto. Así, se o acoplamento producíase durante a fase excitadora de alfa os tempos de reacción eran máis longos e as taxas de acerto máis baixas.

Á vista dos resultados destes cinco estudos experimentais, no presente traballo de doutoramento concluíuse que:

1.- A estrutura temporal dos PE durante a recuperación/recoñecemento de información viso-espacial en MT aseméllase á da codificación de información. Por conseguinte, ambos eventos cognitivos reflíctense en seis compoñentes dos PE (i.e. P1, N1, P2, N2, P300 e unha onda lenta) cunhas latencias e distribución no coiro cabeludo semellantes.

2.- A actividade oscilatoria na banda alfa, e as súas dinámicas (i.e. modulación espectral e sincronía) xogan un papel chave para o mantemento de información viso-espacial en memoria de traballo. Amais, o acoplamento inter-rexional da fase de alfa frontal e a amplitude de gamma posterior constitúe un mecanismo neural que permite a conexión ou desconexión funcional de redes cerebrais de longa distancia durante o mantemento de información en MT.

3.- Unha alta carga en memoria incrementa as demandas cognitivas e a dificultade da tarefa, o que se asocia a peores execucións en tarefas de MT viso-espacial.

4.- As maiores demandas cognitivas impostas por condicións de alta carga en memoria na tarefa de emparellamento demorado modularon o recrutamento de recursos das redes cerebrais fronto-parietal (relevante para a tarefa) e de repouso (irrelevante para a tarefa). En particular, reduciron a activación de áreas frontais da rede irrelevante durante a codificación e a recuperación/recoñecemento, así como tamén reduciron a inhibición das areas relevantes para a tarefa a través de mecanismos de control executivo "arriba-abaixo" durante o mantemento de información.

5.- Unha alta carga en memoria tamén relacionase cunha redistribución dos recursos de procesamento dispoñibles. Dita redistribución manifestase como unha redución dos recursos de procesamento dispoñibles para a categorización do estímulo en favor de procesos de elaboración e mantemento activo da información durante a codificación e da avaliación do estímulo durante a recuperación/recoñecemento en MT.

6.- O incremento da duración do período de mantemento asociase a un incremento na asignación de recursos a procesos perceptivos e de avaliación dos estímulos durante a recuperación/recoñecemento de información, na ausencia de modulacións da execución condutual.

7.- O avellentamento normal acompañase dun declive na memoria de traballo viso-espacial, reflectido en peores execucións da tarefa experimental.

8.- O avellentamento san relacionase cunha diminución na velocidade de procesamento restrinxida á avaliación de características e estímulos relevantes durante a codificación e á avaliación e comparación de estímulos durante a recuperación/recoñecemento de información.

9.- A maior idade, hai menor cantidade de recursos de procesamento dispoñibles e ou adicados á detección das características relevantes do estímulo así como á categorización e procesos post-categorización do estímulo durante a codificación de información.

10.- O avellentamento normal acompañase dunha maior dependencia dos recursos frontais con respecto os posteriores durante a recuperación/recoñecemento. Isto estende a hipótese do desprazamento de rexións posteriores a anteriores coa idade (PASA polas siglas en inglés) á recuperación de información viso-espacial en MT.

11.- Os adultos maiores mostran signos de esforzo cognitivo a menores niveis de carga en memoria que os mozos. Amais, ó contrario do que pasa nos mozos, a execución dos adultos maiores empeora coa carga en memoria. Ambos feitos apoian unha redución da capacidade da MT asociada á idade así como a hipótese do andamiaxe neurocognitivo.

12.- O avellentamento san asociase con alteracións no acoplamento da fase de alfa co amplitude de gamma en redes neurais de longa distancia, o que indica un déficit inhibitoria manifestado como unha conexión ineficiente da actividade de áreas da rede cerebral irrelevante para a tarefa durante o mantemento de información viso-espacial en MT. Ademais, esta conexión ineficiente da rede irrelevante para a tarefa relacionase co declive da execución condutual asociado á idade.

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA