UNIVERSIDAD COMPLUTENSE DE MADRID

**FACULTAD DE PSICOLOGÍA**

**Departamento de Psicología Básica II**

# BRAIN OSCILLATIONS UNDERLYING MEMORY RETENTION AND FORGETTING, IN THE PRESENCE AND ABSENCE OF INTERFERENCE, IN MILD COGNITIVE IMPAIRMENT.
# OSCILACIONES CEREBRALES SUBYACENTES AL MANTENIMIENTO Y OLVIDO DE MEMORIA, EN PRESENCIA Y AUSENCIA DE INTERFERENCIA EN DETERIORO COGNITIVO LEVE

**MEMORIA PARA OPTAR AL GRADO DE DOCTOR**
**PRESENTADA POR**

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Bajo la dirección de los doctores

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**MADRID, 2013**

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**Ph. D. Thesis**


**Sara Aurtenetxe Bikandi**


**Madrid, June 2013**

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## EN DETERIORO COGNITIVE LEVE


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*A Ama y Aita*

*A las Ninas, y los Ninos*

# Acknowledgements

La presente tesis es el resultado del inestimable trabajo y entusiasmo de un gran número de personas. Muestra, por tanto, el resultado de la precisa y coordinada actividad de conjuntos de neuronas distribuidas en un espacio y tiempo determinado.

En primer lugar quiero dar las gracias a mis directores de tesis. A Fernando Maestú por mostrarme el apasionante mundo del envejecimiento, por transmitirme su entusiasmo por la investigación y por su inestimable apoyo durante todos estos años. Muchísimas gracias por hacer que este proyecto haya sido posible y por hacerme sentir como en casa. A Nazareth Castellanos, Naza, por su gran apoyo incondicional, tanto en el ámbito profesional como en el personal, por sus sabias enseñanzas y por su dedicación en mostrarme siempre tan pacientemente la naturaleza oscilatoria de nuestros ritmos cerebrales. A Garikoitz Beitia por su gran ayuda durante todo este tiempo y por mostrarme su entusiasmo por el conocimiento.

Gracias a todo el grupo de Magnetoencefalografía:

A Javi, por su gran amistad y por transmitirme que la paciencia es un! grado de sabiduría; a Pablo por su inestimable apoyo durante todo este trayecto y por transmitirme su entusiasmo y sabiduría. Gracias por mostrarme la importancia del tiempo. A Ricardo, Low, por ser parte de mi familia, por su apoyo incondicional y por enseñarme la importancia de la precisión y coordinación de nuestra actividad neuronal. Al Dr. David, por su ayuda incondicional y por sus siempre acertados consejos. A Maria Eugenia, por todos esos momentos MEG y por mostrarme los beneficios de una buena organización. Espero no olvidemos “pulsar el botón!”. Ángeles, por tener siempre una sonrisa, incluso un chiste, dispuestos a alegrar cualquier situación. A Pilar por su transmisión de calma, siempre eficiente apoyo y amplísima paciencia. A Maria Grazia por habernos alegrado durante todos estos meses. A Juan, por estar siempre dispuesto a escuchar y a ayudar para cualquier ámbito. A Bruña, por estar siempre tan amablemente dispuesto a echar una mano y enseñarnos nuevos términos semánticos. A David, por transmitirme su entusiasmo por aprender y querer siempre ayudar. A Nacho, por sus imparables nuevas y buenas ideas. A Alberto por enseñarnos a actuar con cautela y por su gran apoyo. A Paco, por su siempre tan agradable compañía. A Stephan por adentrarnos en excursiones por el campo y Ángel por sus enseñanzas reconstructivas. A Ricardo Gutiérrez y Guiomar por ayudarnos a entender los famosos bucles. A Gema por su amable ayuda con “las

caras", Ana Bea, Jose, Tino, Sandra y nuevas incorporaciones por su inestimable compañía y apoyo.

También quiero agradecer a Elena, Cristina, Evgenia, Laura, Montse, Alejandra, y Almudena por ser parte fundamental de este trayecto.

Además, agradezco a todos los profesionales del Hospital Clínico, la Unidad de Memoria, del Centro de Día de Chamartín y el Hospital Ramón y Cajal por su gran contribución al proyecto que hemos desarrollado durante este periodo. Además agradezco a Bizitzen Fundazioa por su ayuda en el inicio de este proyecto.

Agradezco a todos los participantes del estudio su inestimable amabilidad y tiempo empleado en este proyecto.

En este punto agradezco enormemente a mi familia por su siempre incondicional apoyo, escucha y dedicación. Por todos esos trayectos de viernes y domingos por la tarde. A Aita, Ama, Mery, Begoñita, Christian, Aitite y las Amamas por sus sabios consejos y por transmitirme siempre tanta alegría y energía. Eskerrik asko!

Agradezco también a mis amigas Aitzi, Agi, Ane, Bego, Eri, Ira, Maia y Nile por todos esos momentazos vividos. Por las largas conversaciones y por su siempre incondicional apoyo. Y por escucharme tanto, y tantas veces. Eskerrik asko neskak.

Por último, Agradezco al Gobierno Vasco por ofrecerme la financiación que me ha permitido desarrollar este proyecto.

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**Aurtenetxe S**, García-Pacios J, del Río D, López ME, Marcos A, Delgado ML, Beitia G, Maestú F. *Interference modulates working memory in mild cognitive impairment.* Under 2º review.

**Aurtenetxe S,** López ME, Bajo R, Garcés P, Cuesta P, P.Castellanos N, Niso G, Pereda E, Maestú F. *Cognitive reserve benefits the organization of the brain functional networks in healthy aging.* Under review.

López M.E., Cuesta P., Garcés P., Castellanos P.N., **Aurtenetxe S**., Bajo R., Marcos A., Delgado M., Montejo P. o Montenegro M., López J.L., Maestú F., Fernández A. MEG spectral analysis in subtypes of Mild Cognitive Impairment. Under review.

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Bajo R, Castellanos NP, López ME, Ruiz JM, Montejo P, Montenegro M, Llanero M, Gil P, Yubero R, Baykova E, Paul N, **Aurtenetxe S**, Del Pozo F, Maestu F. *Early dysfunction o functional connectivity in healthy elderly with subjective memory complaints.* Age. 2012

# Glossary of abbreviations of the main terms

| | |
|---|---|
| ACC | Accuracy |
| AD | Alzheimer's disease |
| ANOVA | Analysis of variance |
| CNT | Control |
| DIS1/2 | Distraction condition under load 1/2 |
| EEG | Electroencephalography |
| fMRI | Functional magnetic resonance imaging |
| INT1/2 | Interruption condition under load 1/2 |
| ICA | Independent component analysis |
| MCI | Mild cognitive impairment |
| MEG | Magnetoencephalography |
| MMSE | Minimental state examination |
| MRI | Magnetic resonance imaging |
| MTL | Medial temporal lobe |
| NI1/2 | No interference condition under load 1/2 |
| NINCDS – ADRA | National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Asociation |
| PET | Positron Emission Tomography |
| PFC | Prefrontal cortex |
| RT | Reaction time |
| SPSS | Statistical Package for the Social Sciences |
| SPECT | *Single-photon emission computed tomography* |
| STD | Standard deviation |
| TFR | Time-frequency |
| wICA | Wavelet- Independent component analysis |
| WM | Working memory |

# Contents

# Summary


## INTRODUCTION

Mild cognitive impairment, MCI, has been proposed as a transitional stage of cognitive decline preceding Alzheimer's disease, AD, (Dubois et al., 2010). Due to the high prevalence of dementia developing from MCI (Petersen et al., 1999), a deeper comprehension of the underlying cognitive features is one of the major topics of pathological aging research.

The most common clinical symptom of MCI is episodic memory loss, in particular, a rapid rate of forgetting and impaired delayed recall, which have been linked to well-known AD neuropathology in medial temporal structures of the brain, such as the hippocampus and entorhinal cortex (Braak et al., 1993). However, recent studies suggest that, besides episodic memory deficits, AD-related processes are characterised by additional impairment in executive functions that are linked to early neurobiological changes in the prefrontal cortex and/or to possible disconnection between brain regions (Perry & Hodges, 1999; Grady et al., 2001; Grambaite et al., 2011; Johns et al., 2012).

There is increasing evidence correlating age-related memory deficits with reduced executive functions, such as the ability to regulate external interference (Jonides et al., 2000; Darowski et al., 2008; Healey et al., 2008). The inhibitory model proposed by Hasher & Zacks (1988) postulates that an inability to ignore or control distracting information underlies cognitive deficits in aging.

Research focused on the study of the impact of interference on aging memory has recently differentiated two general categories of interfering stimuli based on cognitive demands (Clapp & Gazzaley, 2012): *Distraction* refers to irrelevant stimuli that need to be ignored (e.g., ignoring a fly while studying), whereas *Interruption* refers to stimuli

that demand additional processing as a secondary task (also considered multitasking, e.g., attending to a phone-call while cooking; Salvucci & Taatgen, 2008). Along these lines, the disruption of memory by distraction has been attributed to deficits in inhibitory control, whereas the disruption of memory by interruption has been attributed to deficits in shifting attention between two concurrent tasks, also referred to as task-switching. Thus, it appears important to take into account the potential impact of these deficits on memory in pathologies such as MCI.

Difficulties to maintain and manipulate information during brief periods of time (involving the working memory, WM, construct) have been traditionally observed in AD and in MCI across a variety of procedures such as span for words, letters and digits, and through adapted experimental paradigms (Belleville et al., 2007; see Huntley & Howard, 2010, for a neuropsychological review). Additionally, recent reports in the MCI and AD literature reveal difficulties in cognitive control abilities, such as inhibition (for review see Amieva et al., 2004a) and attentional-switching (Belleville et al., 2008; Clément et al., 2012). Furthermore, studies analysing the interference resolution capacity in pathological aging describe vulnerability to interference in MCI and AD, most likely due to deficits in the above-mentioned cognitive processes (Amieva et al., 2004b; Belleville et al., 2006; Bélanger & Belleville, 2009). Thus, it is likely that these deficits could be causing, or at least influencing, the memory alterations observed in MCI.

Although the evidence is not extensive, certain studies have investigated the effect of interference in WM tasks in MCI patients. In this vein, Deiber et al. (2011) used electroencephalography (EEG) to explore the short-term memory of single- and multi-domain MCI patients who were ignoring distraction. The results revealed a higher vulnerability to interference in patients with greater cognitive impairment. In a similar manner, Alescio-Lautier et al., (2007) observed a difficulty in dividing attention between interference and memory probe stimuli in MCI and AD patients. These results are confirmed by Belleville et al., (2007), who revealed a reduction in the memory accuracy of AD and MCI patients, compared to controls, when the subjects simultaneously performed two concurrent tasks.

Overall, the existing evidence reveals that MCI is characterised by deficits in executive processes and specifically, in interference resolution. However, there is no extensive literature examining the effect of interference in WM forgetting under MCI, and more importantly, the joint impact of distraction and interruption in this population has not been investigated.

Cognitive functions are represented by the dynamical synchronous activity of local and distributed cell assemblies in the brain (Siegel et al., 2012). The precise timing of neurons results in oscillatory activity across the frequency range, which traditionally has been divided in five main bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz) and gamma (>30 Hz).

Today, one of the main non-invasive neurophysiological systems that allow studying brain oscillatory activity is the magnetoencephalography (MEG). The main advantage of MEG is its high temporal resolution detecting changes in activity occurring over a few milliseconds. This is of extremely importance when studying cognition since cognitive processes depend on the precise timing of neuronal firing (Varela et al., 2001). Therefore, due to the relevant role of the oscillatory activity in functional communication of the brain, deviations from normal patterns are good candidates to study brain-related pathologies (Schnitzler and Gross, 2005).

Below a summary of the aims, hypothesis, results and conclusions o each of the three experiments of the current Thesis.

## Experiment I

**Objectives.** The aims of the first experiment were to study: 1) how WM maintenance is modulated by interference (distraction and interruption) in patients with MCI, and 2) the impact of WM load under high and low cognitive demands (no interference, distraction and interruption conditions) in this population.

**Hypothesis.** In the first experiment were expected that: 1) interruption will cause more forgetting than distraction, being more pronounced in the MCI than in the control

group, and 2) memory load will reduce performance in all of the conditions, with a more pronounced impact in the MCI participants.

**Methods.** A total of 40 volunteers participated in the study. 20 were diagnosed as amnesic-multidomain MCI patients and 20 were diagnosed as healthy controls. Participants performed a delayed recognition WM paradigm with three interference conditions: no interference (NI), distraction (DIS) and interruption (INT) under two memory loads (1 and 2 items to memorise). A three-way repeated measures ANOVA was performed to evaluate performance of participants.

**Results.** This experiment revealed a progressive reduction in accuracy as the demands of the conditions increased (from NI to DIS and INT). These results were more prominent in MCI patients than in healthy controls. The presence of interruption was the most devastating for memory, especially in the MCI patients.

**Discussion**. Difficuties to handle interference during WM maintenance is a fundamental aspect of memory failures in MCI patients, with a heavy impact of high demanding interference as is interruption. We are able to conclude that WM forgetting in MCI potentially stems from deficits in executive processing.

## Experiment II

**Objectives.** The aim of the second experiment was to study the oscillatory mechanisms supporting successful WM maintenance in MCI patients, as well as their relation with hippocampal volumes

**Hypothesis**. In the second experiment, we expected brain oscillatory deviations from normal patterns, in MCI patients. Increased oscillatory activity was expected to be related with improved task accuracy and with higher hippocampal volumes, whereas reduced activity will reflect a reduction in accuracy and with reduced hippocampal volumes.

**Methods**. A total of 73 volunteers were included in the study. 39 were diagnosed as amnesic-multidomain MCI patients and 34 were diagnosed as healthy controls. Brain

activity was recorded with MEG during the execution of a WM delayed recognition task (without interference). Analysis was focused on the retention period of correct responses of the task. Analysis of the MEG signals involved an independent component analysis and a time-frequency estimation of the components.

**Results**. This experiment revealed, under the same WM accuracy between groups, increased power of theta and alpha frequency bands during memory retention in MCI patients, in comparison with healthy controls. These activity increases were related with reduced hippocampal volumes.

**Discussion**. Increased power of alpha frequency band seems to be associated with a progression of the pathology in the MCI brain leading to decrease in performance. Theta band increase seems reflect a necessary mechanism to maintain high cognitive performance.

## Experiment III

**Objectives**. The aim of the third experiment was to study the oscillatory WM maintenance patterns underlying successful and non-successful memory maintenance in the presence of interruption in MCI patients, as well as their relation with hippocampal volume of participants.

**Hypothesis**. In the third experiment, we expected reduced accuracy in MCI patients comparing with controls. Successful WM retention will be related with increased oscillatory activity and higher hippocampal volumes in MCI patients. Contrary, WM forgetting will be related with reduced oscillatory activity and with reduced hippocampal volumes.

**Methods**. A total of 44 volunteers participanted in the study. 22 were diagnosed as amnesic-multidomain MCI patients and 22 were diagnosed as healthy controls. Brain activity was recorded with MEG during the execution of a WM delayed recognition task with interruption. Analysis was focused on correct and incorrect trials separately. The periods of interest involved the pre and post interference retention periods of the

task. Analysis of the MEG signals involved an independent component analysis and a time-frequency estimation of the components.

**Results**. The group of patients showed reduced memory accuracy than controls. This experiment revealed that interference modulated brain oscillatory activity in both groups of participants. MCI patients showed, comparing with controls, higher theta and alpha power values for accurate responses and reduced theta and increased alpha power for errors.

**Discussion**. While maintaining sensory information in WM, activity in the theta frequency band is modulated by interference in MCI patients. This modulation seems to be responsible for successful memory and for forgetting of information in this population. Modulation of alpha frequency band points to be related with brain pathological processes characterizing the MCI population.

# Resumen

## INTRODUCCIÓN

El deterioro cognitivo leve (DCL), ha sido propuesto un estado de transición de deterioro cognitivo que precede a la enfermedad de Alheimer, EA, (Dubois et al., 2010). Dada la altea prevalencia del DCL a desarrollar EA (Petersen et al., 1999), una comprensión más profunda sobre las características cognitivas que lo subyace es uno de los mayores temas de investigación en envejecimiento patológico.

El síntoma clínico más común en el DCL es la pérdida de memoria episódica. En particular, un alto grado de olvido y alteración de recuerdo demorado, que se ha relacionado con la ya reconocida neuropatología de la EA en estructuras mediales del lóbulo temporal cerebral, como el hipocampo y la corteza entorrinal (Braak et al., 1993). Aun así, estudios recientes muestran que, además de déficits de memoria episódica, los procesos relacionados con la EA se caracterizan también por alteraciones adicionales en funciones ejecutivas que están relacionadas con cambios neurobiológicos tempranos en el cortex prefrontal y/o con posibles desconexiones entre regiones cerebrales (Perry & Hodges, 1999; Grady et al., 2001; Grambaite et al., 2011; Johns et al., 2012).

Existe evidencia que correlaciona las alteraciones de memoria en el envejecimiento con una reducida habilidad en funciones ejecutivas, como la habilidad para regular interferencia externa (Jonides et al., 2000; Darowski et al., 2008; Healey et al., 2008). El modelo inhibitorio propuesto por Hasher & Zacks (1988) postula que la inhabilidad para ignorar o controlar información distractora es lo que subyace los déficit cognitivos en el envejecimiento.

La investigación enfocada en el estudio del impacto de la interferencia en la memoria en el envejecimiento ha diferenciado recientemente dos categorías generales de

estímulos de interferencia, que se basan en las demandas cognitivas de cada uno de ellos (Clapp & Gazzaley, 2012): D*istracción* se refiere a estímulos irrelevante que requieren ser ignorados (p.ej., ignorar una mosca mientras se estudia), mientras que *Interrupción* hace referencia a estímulos que demandan un procesamiento adicional como tarea secundaria (también considerada multi-tarea, p.ej., atender una llamada telefónica mientras se cocina; Salvucci & Taatgen, 2008). De este modo, la alteración de memoria por distracción se ha relacionado con dificultades en control inhibitorio, mientras que la alteración de memoria por interrupción se ha relacionado con dificultades para cambiar el foco atencional entre dos tareas simultáneas, también llamada cambio de tarea. Por lo tanto, es importante tener en cuenta el impacto que estos déficits podrían tener sobre la memoria en patologías como el DCL.

Dificultades para mantener y manipular información durante periodos cortos de tiempo (lo que conlleva el concepto de memoria operativa, MO) se han observado en EA y DCL tradicionalmente a lo largo de varios procedimientos como span para palabras, letras y dígitos, y mediante paradigmas experimentales adaptados (Belleville y cols., 2007; ver Huntley & Howard, 2010, para una revisión neuropsicológica). De manera adicional, estudios recientes enla literatura de EA y DCL muestran alteraciones en habilidades de control cognitivo, como inhibición (para revisión ver Amieva y cols., 2004a) y cambio atencional (Belleville y cols., 2008; Clément y cols., 2012). Además, estudios que analizan la capacidad de resolución de interferencia en envejecimiento patológico describen vulnerabilidad a interferencia en EA y MCI, mayoritariamente debido a los déficits mencionados (Amieva y cols., 2004b; Belleville y cols., 2006; Bélanger & Belleville, 2009). Por tanto, parece evidente estas alteraciones pueden causar, o por lo menos influenciar en, las alteraciones de memoria que se observan en el DCL.

A pesar de que la evidencia no es extensa, ciertos estudios han investigado el efecto de la interferencia en la MT en pacientes con DCL. Para estudiar esta posible relación, Deiber y cols., (2011) exploraron, mediante electroencefalografía (EEG) la memoria a corto plazo de pacientes con DCL mono y multidominio mientras debían ignorar estímulos distractores. Los resultados mostraron mayor vulnerabilidad a la interferencia en pacientes con mayor deterioro cognitivo. De manera similar, Alescio-

Lautier y cols., (2007) observaron dificultades para dividir la atención entre interferencia y estímulos que debían memorizar pacientes con DCL y EA. Estos resultados son confirmados por Belleville y cols., (2007), quienes demostraron reduccion en la capacidad de memoria en pacientes con EA y DCL, en comparación con controles, cuando los sujetos realizaban dos tareas simultáneamente.

En general, la evidencia existente muestra que el DCL se caracteriza por déficits ejecutivos, y específicamente en resolución de interferencia. Aun así, no existe ámplia evidencia que estudie el efecto de la interferencia en el olvido de MO en DCL, y de manera más importante, el estudio del efecto de la distracción y la interrupción de manera conjunta en esta población no ha sido estudiado.

Las funciones cognitivas están representadas por la actividad dinámica sincronizada de conjunto de neuronas locales y distribuidas en nuestro cerebro (Siegel y cols., 2012). El ritmo preciso de neuronas results en actividad oscilatoria a lo largo del rango de frecuencias, que tradicionalmente ha sido dividido en cinco bandas principales: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz) y gamma (>30 Hz).

Actualmente, uno de los sistemas neurofisiológicos no-invasiviso que permite estudiar la actividad oscilatoria cerebral es la magnetoencefalografía (MEG). La mayor característica de la MEG es su alta resolución temporal para detectar cambios de actividad en milisegundos. Esto es de gran importancia al estudiar la cognición ya qye los procesos cognitivos dependen del ritmo preciso de los disparos neuronales (Varela y cols., 2001). Por lo tanto, dada la relevancia de la actividad oscilatoria en la comunicación funcional de nuestro cerebro, el estudio de desviaciones desde patrones estándar ofrece una buena vía para estudiar patologías cerebrales (Schnitzler y Gross, 2005).

A continuación un resumen de los objetivos, hipótesis, resultados y conclusiones de cada uno de los tres experimentos de la presente Tesis.

**Experimento I**

**Objetivos.** Los objetivos ddel primer experiemtno fueron estudiar: 1) cómo la MO es modulada por la interferencia (distracción e interrupción) en pacientes con DCL, y 2) el efecto de la carga en MO ante alta y baja demanda cognitiva (no interferencia, distracción e interrupción) en esta población.

Hipótesis. En el primer experimento esperamos que: 1) la interrupción causará mayor olvido que la distracción, y será más pronunciado en DCLs que en controles sanos, y 2) la carga de memoria reducirá la ejecución a lo largo de todas las condiciones, con mayor impacto en el grupo de pacientes.

**Métodos**. 40 voluntarios participaron en el estudio. 20 fuerosn diagnosticados como DLC amnésico-multidominio, y 20 fueron diagnosticados como controles sanos. Los participantes realizaron un paradigma de MO de recuerdo demorado bajo tres condiciones experiementales: no interferencia (NI), distracción (DIS) e interrupción (INT) bajo dos cargas de memoria (1 y 2 ítems a memorizar). Para estudiar la ejecución de los participantes, se realizó un ANOVA de tres factores.

**Resultados**. Este primer experimento mostró una reducción progresiva de memoria deacuerdo al incremento de demandas cognitivas (desde NI hasta DIS e INT). Este efecto fué mayor en pacientes quee en controles. La interrupción fue la condición que provocó mayor reducción de memoria, especialmente en el grupo de pacientes.

**Discusión**. Las dificultades para manejar interferencia durante el mantenimiento de MW es un aspect fundamental en la alteración de memoria en pacientes con DCL, con un mayor impacto de interferencia altamente demandante, como es la interrupción. Concluimos que el olvido de MO en DCL está potencialmente causado por déficits en procesamiento ejecutivo.

**Experimento II**

**Objetivos**. El objetivo principal del Segundo experimento fue estudiar los mecanismos oscilatorios que sustentan el mantenimiento exitoso de MO en pacientes con DCL, así como su relación con el volumen de hipocampo.

**Hipótesis**. En el segundo experimento esperamos observar patrones de actividad desviada en el grupo de pacientes. Un incremento en actividad estará relacionada con una mejora en la ejecución y mayor volumen de hipocampo, mientras que la reducción en actividad reflejará una menor ejecución y menor volumen de hipocampo.

**Métodos**. Un total de 73 volunatios participaron en el estudio. 39 fueron diagnosticados como MC amnésicos-multidominio y 34 fueron diagnosticados como controles sanos. Se registró la actividad cerebral mediante MEG mientras los participantes realizaban una tarea de MO de reconocimiento demorado (sin interferencia). El análisis se focalizó en el periodo de mantenimiento respuestas correctas de la tarea. El análisis de las señales MEG incluyó un análisis de componentes independientes y la estimación del tiempo-frecuencia de los componentes.

**Resultados**. Este experimento mostró, ante la misma ejecución entre grupos, un incremento de potencia en las bandas de frecuencia theta y alpha durante el periodo de mantenimiento en el grupo de DCls, en comparación con el grupo control. El incremento de actividad se mostró relacionado con menor volumen de hipocampo.

**Discusión**. El incremento de potencia en alpha señala su relación con la pregresión de la patología en el cerebro del grupo con DCL, que provoca una reducción en ejecución. Por el contrario, el incremento de la potencia de la banda theta parece mostrar un mecanismo para mantener un alto grado de ejecución.

**Experimento III**

**Objetivos**. El objetivo principal del tercer experimento fue estudiar los patrones de actividad oscilatoria que sustentan una MO exitosa y fallida en presencia de interferencia en pacientes con DCL, así como su relación con el volumen de hipocampo de los participantes.

**Hipótesis**. En el tercer experimento, esperamos una reducción de ejecución en pacientes con DCL, en caparación con la ejecución de los controles. El mantenimeinto exitoso de MO se relacionará con mayor actividad oscilatoria y mayor volumen de hipocampo en el grupo de pacientes. Por el contrario, el olvido de MO se relacionará con una reducción de la actividad oscilatoria y mayor atrofia de hipocampo.

**Métodos**. Un total de 44 personas participaron en el estudio. 22 fueron diagnosticados como MC amnésicos-multidominio y 22 fueron diagnosticados como controles sanos. Se registró la actividad cerebral mediante MEG mientras los participantes realizaban una tarea de MO de reconocimiento demorado con interrupción. El análisis se focalizó en el periodo de mantenimiento pre y post interferencia, separadamente, de respuestas correctas e incorrectas. El análisis de las señales MEG incluyó un análisis de componentes independientes y la estimación del tiempo-frecuencia de los componentes.

**Resultados**. El grupo de pacientes mostró menor tasa de aciertos que el grupo de controles. Este experimento mostró que la interferencia modula la actividad oscilatoria en ambos grupos de mayores. Aun así, los DCL muestran mayores valores de theta y alpha que el grupo de controles durante un mantenimiento exitoso. De manera contraria, durante un mantenimiento fallido, la actividad de la banda theta es reducida en el periodo después de la interferencia.

**Discusión**. Durante el mantenimiento de información sensorial en MO, la actividad en la banda theta es modulada por la interferencia en pacientes con DCL. Esta modulación apunta a ser la responsable de un mantenimiento tanto exitoso como fallido en esta población. La modulación de alpha indica, como en el experimento anterior, el posible proceso patológico que subyace a la población DCL.

# Overview

The present Thesis aims to study how external interference affects brain oscillatory activity during working memory (WM) retention in mild cognitive impairment (MCI). The first Chapter exposes an introduction to the state of the art on the topic. The second Chapter describes the objectives and hypothesis of the present Thesis. The third Chapter describes the first experiment of the present Thesis, in which the impact of the two main interference stimuli (distraction and interruption) on WM retention in MCI are analyzed under two different memory loads. The fourth Chapter describes the second experiment, in which the oscillatory activity underlying successful WM retention in MCI is studied. The fifth Chapter describes the third experiment, in which the oscillatory activity underlying correct and incorrect WM retention in the presence of interruption in MCI is studied. The sixth Chapter exposes the main conclusions of the Thesis and future directions.

# CHAPTER 1. Introduction

# 1. ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT

Current development of science and its advances have improved the quality of life in today's society and thus, have contributed to the increase on life expectancy. This fact has increased the prevalence of dementia, defined as a progressive or chronic, cortical and/or subcortical, dysfunction of the central nervous system which alters the cognitive functions and therefore the activities of daily life living of humans.

Dementia rates augment as a function of age, affecting 5% of the population older than 65 and 20–40% of those older than 85. Recent statistics reveal that the total number of people with dementia is projected to almost double every 20 years, from 35.6 million in 2010 to 65.7 million in 2030 (source: World Health Organization).

Nowadays, the most known types of dementia are Alzheimer's disease, Vascular dementia, dementia with Lewy bodies, mixed dementia, Parkinson's dementia, fronto-temporal dementia and Hungtinton's dementia. Under this classification, Alzheimer's disease (AD) is considered the most common form of dementia, accounting between the 50%-80% of dementia cases worldwide. Further, the interest in the study of AD has increased in recent decades as its prevalence increases by two every five years of age: 1.4% between 65 and 69 years and 23.6% in the population over 85 years old (Jorm et al., 1987). Due to its prevalence and incidence, and to the consequent individual and social impact, its early identification has become one of the main goals of dementia research.

Mild cognitive impairment (MCI) has been proposed to represent the border zone between normal aging and dementia (Flicker et al., 1991, Petersen et al., 1999, 2004). It has been estimated to affect 10-17% of the elderly population, and has been considered as a major precursor of Alzheimer's disease since the conversion rate of MCI to dementia is 10-15% per year, while of those with normal aging is a 1-2% (Petersen, 2004; see Twamley et al., (2006) for a review of neuropsychological and

neuroimaging literature on preclinical AD). Thus, studying clinical and brain features that characterize MCI patients is one of the major goals of dementia research.

## 1.1. Structural and functional features

First described in 1906 by the German psychiatrist and neuropathologist Alois Alzheimer, the neuropathology of AD is characterized by: the presence of extracellular plaques of beta-amyloid protein and intracellular accumulation of neurofibrillary tangles, NFTs, neuronal and synaptic loss, and brain atrophy (Decarli, 2001; Selkoe, 1994).

*Dr. Alois Alzheimer*

The neuropathology of AD emerges in the patient's brain even decades before any clinical symptom manifests. Considering MCI as a gate preceding AD, neuropathological, structural and functional changes which are intermediate between normal aging and AD have been described in the MCI pathology (see Markesbery, 2010 for review of longitudinal studies).

The brain pathology is translated into structural and functional brain damage, mainly involving regions where the concentration of pathology is the greatest (see Morrison and Holf, 1997 for a review). The presence and progression of these alterations in the brain are indirectly observable in vivo (Jack et al., 2002; Gosche et al., 2002; Silbert et al., 2003) trough imaging techniques. The earliest morphological changes that predict in AD usually involve hippocampal and parahippocampal regions and entorhinal cortex, in addition to the brain volume (see Braak et al., 1993 for review).

According to the involvement of the medial temporal structures in the process to AD, the most common first symptom of pathology has been related with difficulties in episodic memory (Welsh et al., 1992). The structures that best discriminate AD patients and healthy adults are hippocampus, temporal and parietal cortices (Zakzanis et al., 2003). Additionally, overall brain atrophy and enlargement of the ventricles also characterize the AD brain.

As the disease advances, the neuropathology spreads into distributed cortical areas additional areas of the neocortex, such as cortical association areas giving rise to additional cognitive deficits in attention, praxis, communication skills, reasoning, behavior and emotional status (Nestor et al., 2004).

MCI patients destined to develop AD show reduced grey matter volume, higher degree of atrophy in MTL, posterior cingulate, lateral temporal and parietal cortex compared with healthy or stable MCI patients. Measurements of GM volume loss predict conversion from MCI to AD (Whitwell et al., 2007) and interestingly, atrophy in the MTL and particularly in hippocampus has been recently proposed as a possible marker of incipient AD (Dubois et al., 2007; Frisoni et al., 2010). Additional alterations are also observed in prefrontal cortex (PFC) regions and between distributed brain networks in MCI patients (Delbeuck et al., 2003; Gili et al., 2010; see Maillet et al., 2013), which explain additional early clinical symptoms such as difficulties in attentional control.

Functional imaging studies, such as positron emission tomography (PET) or single photon emission computerized tomography (SPECT) show progressive reduced blood flow and hypometabolism in posteror cingulate gyrus, precuneus, medial temporal structures and parietal-temporal association cortex years before the clinical manifestations of AD (Matsuda, 2001; Mosconi, 2005; Mosconi et al., 2009).
Additionally, functional magnetic resonance imaging (fMRI) research shows task-related functional deactivations and over-activations typically in MTL, parietal and frontal regions of the brain and altered distributed connectivity throughout the entire brain. These activity patterns differ from normal aging to MCI and AD, and depend on the difficulty and modality of the task. Brain hypo-activation in AD related pathology has been traditionally related with pathological accumulation and neuronal loss and on consequence, with reduction of cognitive capacity. Contrary, brain over-activations (mainly in prefrontal regions and contralateral to the hemisphere supporting a specific cognitive process) have been interpreted as reflecting dedifferentiation of specialized brain regions or compensation of brain pathology, which allows maintaining certain level of cognitive performance (Reuter-Lorenz, 2002; Grady, 2012; will be described later more in detail).

## 1.2. Diagnosis

### 1.2.1. Alzheimer's disease

NINCDS – ADRA criteria (McKhann et al., 1984) establish that when deficits in two or more areas of cognition (including memory) are progressive and become severe enough to interfere with daily living activities (without disturbance of consciousness and any other brain pathology which could account for the deficits) is sufficient criteria to establish a clinical diagnosis of probable AD.

As stated by the National Institute of Health, 1987: *The best diagnostic test is a careful history and physical and mental status examination by a physician with knowledge of and interest in dementia and the dementing disease. Such an evaluation is time consuming, but nothing can replace it*. As this statement postulates, a correct diagnosis of AD in-vivo depends on knowledge, experience and time. It is therefore, critically dependent to the subjectivity of the physician. Accordingly, discriminating the initial manifestations of AD from the cognitive changes that accompany normal aging is sometimes challenging and one of the main goals for management and treatment purposes.

Nowadays, an in-vivo diagnosis of dementia is limited to diagnose *Probable AD* because the definite AD diagnosis can nowadays, only be established port-mortem through histopathological examination of the brain tissue (as proposed by the Consortium to Establish a Registry for Alzheimer's Disease, CERAD, in 1991). This criterion is based on the quantification of neuritic plaques in the frontal, temporal and parietal lobes of the brain, after which an age-related score is determined together with clinical information regarding the presence or absence dementia of the person in life.

In an attempt to improve diagnosis in vivo, the International Working Group New Research Criteria for the Diagnosis of AD recently has moved beyond the NINCDS –

ADRA criteria and has proposed a new diagnostic framework (Dubois et al., 2007). Headed by Bruno Dubois and motivated by the recent advances in the use of reliable biomarkers evidencing the disease, both clinical and in-vivo biological evidence of AD for diagnostic criteria have been included (the nowadays most-validated AD biomarkers involve: reduced amyloid and tau in the cerebrospinal fluid, increased amyloid concentrations in the brain, observable with positron emission tomography, and medial temporal lobe atrophy). In addition to the clinical symptoms necessary for diagnosis, today one positive evidence of the currently validated biomarkers is sufficient to diagnose under this new framework.

These new proposed criteria are nowadays more frequently used in research studies than in clinical practice (although not yet systematically) mainly due to economic and resource reasons. However, one of the future goals is to slightly spread and reach everyday clinical practice.

### 1.2.2. Mild cognitive impairment

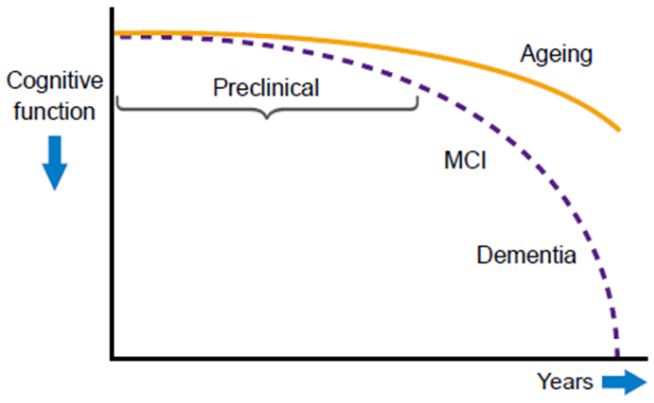
As described by Petersen (2004), MCI is characterized by impaired memory capacity, and/or additional cognitive functions without interfering with the activities of daily living. Early diagnosis and specifically early identification of patients at risk for the development of dementia such as MCI population, is critical in the study of dementia. This would provide effective cognitive and/or pharmacological interventions to slow down the progression of cognitive deficits and retard the onset of dementia. In the Table1.1 there is a graphic description of the clinical criteria for MCI.

| **Clinical criteria for Mild Cognitive Impairment** |
|---|
| 1. Memory complaint, preferably corroborated by an informant<br>2. Objective memory impairment for age and education<br>3. Largely intact general cognitive function<br>4. Essentially preserved activities of daily living<br>5. Not demented |
| Source: Mayo Alzheimer Disease Center and Petersen et al., (1999) |

Research on MCI has evidenced the existence of several clinical subtypes (Petersen, 2001). In this line, two main types of MCI have been described its clinical

heterogeneity: *amnesic-MCI* (involving memory deficits) *and non-amnesic-MCI* (involving deficits other than memory). Each of them can be classified as single and multi-domain: *Single-domain amnesic-MCI* (where memory is affected to a significant degree of 1.5 standard deviations, SD, below age and education matched healthy adults; while other cognitive domains are mildly impaired, 0.5 SD below matched adults); *multiple domain amnesic-MCI* (including additional cognitive impairment than memory, where several cognitive domains are impaired between 0.5 and 1 SD below matched subjects); *single-domain non-amnesic -MCI* (where a cognitive domain other than memory is impaired to a significant degree of 1.5 standard deviations, SD, below matched subjects); *multiple domain non-amnesic-MCI* (where several cognitive domains other than memory are impaired between 0.5 and 1 SD below matched subjects). At present, the most common form of MCI is *amnesic-MCI* with a high conversion rate to AD.

Taking into account the prevalence and incidence the MCI population, and given the impact of this degenerative process on person's life, it is nowadays highly important to study the mechanisms underlying this cognitive depletion, especially on memory, which can help to delineate intervention actions. Below a model of cognitive decline in the AD spectrum proposed by Sperling et al., (1001).




Model of cognitive decline across age (Sperling et al., 2001)

## 2. FORGETTING OUR MEMORIES

As elegantly pointed out by Ruiz-Vargas (2010), *remembering does not seem to be important; just forgetting draws our attention*. As he explains, our memory is persistently retrieving memories but we are not usually aware of it. However, the fail to remember any information causes a very uncomfortable feeling, even if this forgetting is an isolated or even unusual fact.

Memory is what leads us know who we were in the past, who we are at present and who we expect to be in the future. Thus, forgetting our memories, in its maximal expression, would result in forgetting ourselves. Given the aging of the society and the memory decline associated with it, forgetting is one of today's worries. Interventions in cognitive decline and pathology require knowledge of its underlying mechanisms and thus, to disentangle the causes of forgetting is nowadays one of the main focuses of cognitive aging research.

The term *forgetting* can be defined as "the inability to retrieve at present any information which was successfully retrieved in a previous occasion" (Tulving in 1974).

It is important to differentiate two types of forgetting at this point: incidental forgetting (when we do not remember something without any intention to do so; i.e. to do not know where the keys were left), and motivated forgetting (when there is the intention to forget specific information from our memories; i.e. the intention to forget our previous phone number or an unpleasant episode). Based on the main goals of the current Thesis, the study of the mechanisms underlying memory and forgetting in MCI individuals, we will now focus this theoretical framework on the theories underlying incidental forgetting.

## 2.1. The two main theories of forgetting: decay vs. interference-based forgetting

### 2.1.1. Decay theory of forgetting

Based on the forgetting curve established by Ebbinghaus in 1885, the decay theory postulates that is the mere passage of time what eliminates our memories. That is, memory decays over time without additional influence, being information less accessible for its later retrieval.

This theory was largely accepted by the scientific society and was the main argument of memory forgetting for several decades. However, although an experimental testing of the decay hypothesis seems easy, its empirical testing is not straightforward. On one hand, it is experimentally difficult to control for active rehearsals or directing attention towards the memory traces during retention intervals. On the other hand, special attention must be paid to what occurs during the retention period, such as any potential stimulus which can enter into the consciousness of the individual (Overauer and Lewandowsy, 2013).

Several research studies working in the attempt to solve these controversies (Baddeley, 1986; Page & Norris, 1998; Berman et al., 2009) conclude that the mere passage of time is not a consistent argument to explain the cause of forgetting due to the tendency to rehearse during unfilled intervals and to the effect that interference causes when trying to avoid this rehearsal. This opened the door to the question of whether the materials and tasks that occupy the delay time between memory encoding and retrieval might be involved in the forgetting process by interfering with the to-be-retained material (Dewar et al., 2007).

Early in the XX century, alternative explanations about causes of forgetting began to emerge. Already in 1900, Müller and Pilzecker experimentally revealed for the first time the role of interference in forgetting. Further, McGregoch (1932) established a match-point between decay and interference theories by postulating that it is

interference after learning which causes forgetting, rather than the mere passage of time. Basic concepts of interference on memory are discussed below.

### 2.1.2. Interference-based theory of forgetting

The concept of interference in memory refers to any internal or external stimulus which impacts with the information to be retained. Two main types of interference have been studied in the memory literature: proactive interference and retroactive interference (Ruiz-Vargas, 2010).

*Proactive interference, PI,* refers to the tendency of old memories to obstruct retrieving recent information, facts or knowledge (i.e., difficulty to remember a new phone password due to the interference caused by the previous one).

*Retroactive interference, RI,* refers to forgetting of a previous memory caused by the new learning of similar information (Dewar et al., 2007) (i.e., difficulty to remember your old phone password due to the interference caused by the new one). This type of interference is highly feasible in the activities of daily living and plays an essential role in short-term memory consolidation. Experimental research on RI is highly feasible through working memory (WM; the ability to maintain and manipulate information during brief periods of time) paradigms, which allow studying how an upcoming stimulus/information affects the retention of information held in memory.

In this line, forgetting due to interference theory indicates that forgetting our consolidated memories, rather than caused by a mere passage of time, is caused by the presence of interference. Implications of such assumptions on memory deficits-related states are nowadays carefully taking into account for understanding the mechanisms underlying them.

## 2.2. How does interference behave with our memories? How forgetting occurs?

Several theories have been studied aiming to disentangle how forgetting occurs. Below, I will briefly describe the main theories explaining forgetting of consolidated memories.

### 2.2.1. Classic theories of forgetting

Classical theories of forgetting postulate two main non-exclusive causes of forgetting due to interference. The *response competition theory* and the *associative blocking* hypothesis (McGeoch, 1932, 1942). Basically, these hypothesis postulate that in the presence of the same associative cue, the memories associated with this cue compete between each other (interfere between them) trying to access consciousness. Based on this assumption, it is the competition between both memories which difficulties (interferes with) memory retrieval.

However, Melton and Irwin in 1940 showed that the competition of responses was not the only mechanism causing forgetting and added that the associations between a cue A and an associated memory B weakens whenever the cue is retrieved or associated inadequately with competing information C.

Even the importance of both theories on forgetting research, either theories resulted non-conclusive: they do not explain whether the mere fact of the strength of a competitor is able to cause forgetting or if a memory is completely forgotten. This fact emerged alternative explanations about forgetting and leaded to the role of inhibition on memory.

### 2.2.2. New theories of forgetting: the role of inhibition

Inhibition is described as a process which orchestrates cognitive performance in several cognitive domains (Clark, 1996; Amieva, 2004). Inhibition can be defined as an as ensemble of processes which allow the suppression of previously activated cognitive contests, clearance of irrelevant actions or attentional focus from

consciousness, and which allows the resistance to interference from potentially attention-capturing stimuli.

In contrast with the classical theories of forgetting, recent theories hold that much of "our forgetting is caused by inhibitory processes which regulate the access to memories. That is when a memory interferes with another memory or it is not desirable, inhibitory processes alter the activation of the first and reduce its access for the future" (Ruiz-Vargas, 2010). Thus, in the presence of interference, is inhibition which regulates the access to the unwanted memories. In this line, inhibition impedes non desirable memories to access consciousness by overriding non desirable responses and helping to select the desirable ones (Anderson, 2007).

Under this framework, it is assumed that is the cognitive control mechanism (the process of controlling our thoughts and actions, mainly based on inhibition), and no the competition between representations, as postulated by previous theories, which controls interference in memory and forgetting. As Anderson (2008) mentions, overriding the retrieval of unwanted memories induces a lasting suppression of these unwanted memories, making them more difficult to recall later, even when we want to return to them. To understand the dimensions of the role of cognitive control in forgetting, two main experimental paradigms have been developed. The first, evaluates control processes on selective retrieval, and the second studies control processes on stopping retrieval of memories:

*Retrieval Induce Forgetting* (Anderson et al., 1994). This paradigm demonstrates that remembering specific information inhibits and causes forgetting of associated memories. That is, practiced items are more easily remembered at test than no-practiced items. The paradigm involves three main phases. In the study phase participants learn a list of pair-associates. In the second phase they are instructed to retrieve the pair associated of a given cue, while other pairs are not being retrieved. In the third phase they are asked to recall all the studied items. Results from this paradigm indicate that the non-practiced information is forgotten in a higher rate than

the practiced information, suggesting that the retrieval of information causes inhibition of related but non-practiced information.

*Directed Forgetting and Think-no-Think paradigms* (Johnson, 1994; Anderson and Green, 2011). These paradigms demonstrate that inhibitory mechanisms are able to stop retrieval of information, impede unwanted memories to enter consciousness and in consequence, cause forgetting of this information. This paradigm involves three phases. In the first phase participants memorise a list of pair-associate words. In the second phase, depending on the instruction, individuals must say at loud the pair associate of a presented cue or contrary must do not think in the associate word to the cue and must avoid this word to enter into consciousness. The third phase of the task includes a test in which based on a cue, participants must recall the pairs learned on the first phase of the experiment. Results show that participants retrieve significantly less items which were voluntarily suppressed in the second phase than items which did not appeared again but which were learned in the first phase. These results show that suppression of unwanted information alters its memoranda and points out the important role of inhibition in forgetting.

Based on this, it is now largely accepted that inhibition is one of the mechanisms necessary for controlling memory, either for suppressing unwanted memories, either for avoiding information to enter our memories.

The role of inhibition of interference in memory processes is being largely studied through delayed matched to sample working memory paradigms, due their capacity to differentiate between encoding, maintenance and memory recall periods. Under this framework, the present Thesis is focused on the role of interference on WM, and specifically on the role of retroactive interference, because it allows studying non-desirable forgetting (as it accounts in MCI), because it represents a common situation in daily living activities and because it offers high ecologic validity to study memory alterations in MCI. A more detailed description of the role of interference in WM will be offered later.

# 3. COGNITIVE NEUROSCIENCE MODELS OF AGING

## 3.1. Slowing as a global factor

Cognitive processing speed refers to how fast one can execute the mental operations to complete a task. The model of cognitive slowing, proposed first by Kail and Salthouse (1994), postulates that the cognitive alterations accounted in the process off aging reflect a consequence of a general slowing in processing speed (accounted by larger reaction time is cognitive tasks). This hypothesis has been related with affectation of the white matter in the brain due to the role of myelination in signal transmission speed between the neurons (Lu et al., 2011). Thus, the cognitive slowing would be caused by a reduction in the capacity to communicate between the neurons all over the brain. Although a slowing in processing speed is a well-established factor, this model has been criticized due to its simplistic view in reducing the cognitive alterations in aging to a mere alteration of processing speed (Bashore et al., 1997).

## 3.2. Frontal lobe hypothesis and the inhibitory model in cognitive aging

Supported by the early decline of PFC functions that account in aging, the frontal lobe hypothesis in aging postulates that old adults perform worse than their young counterparts in tasks related with cognitive processes that depend on the frontal lobe, specifically on the PFC (West, 1996). Indeed, this model is supported by a reduced performance in aging in tests requiring executive processes, such as attentional control and resolution of interference, and maintenance of sensory representations in memory, when compared with more simple tasks, and when compared with young adults.

Close to this hypothesis, the inhibitory model proposed by Hasher & Zacks (1988) postulates that the cognitive deficits associated with aging are explained by deficits in inhibitory control, that depend on the PFC functions and which play an essential role in

filtering and suppressing irrelevant information and in controlling prepotent responses. As will be described later, deficits in inhibitory processes is today one of the main hypothesis of WM deficits in healthy and pathological aging.

### 3.3. Models based on brain activation

Cognitive capacity changes across time. Further, aging is associated with alterations in brain structure and function, which explains the cognitive decline associated with aging (Reuter-Lorenz, 2002; Dennis and Cabeza, 2008). However, recent literature indicates that, even in old adults, the brain preserves plasticity and reorganization capacities (Grady, 2008). Experimental research in neuroimaging has been enrolled in the comprehension of the brain activity patterns associated with these differences in cognition. In this line, the most characteristic findings during cognitive tasks show brain under-activation and over-activation in old adults when compared with younger counterparts. Brain under-activations have been traditionally related with brain atrophy and/or cognitive capacity reduction, and have been interpreted as a sign of impairment. By contrast, brain over-activations have been traditionally related with dedifferentiation or compensation mechanisms (Reuter-Lorenz and Lustig, 2005; Grady, 2012).

**Dedifferentiation:** refers to a reduction in the selectivity of responses or in the functional differentiation between/within hemispheres/brain regions during cognition that occurs in aging, and which does not imply any specific function (Li and Lindenberger, 1999; Grady, 2012). Experimental research evaluating dedifferentiation shows that: old adults present bilateralization of brain regions which are lateralized in young, reduction of selective activity of brain regions across tasks, similar brain activation under novelty or repetition of stimuli and diffuse brain activity patterns.

**Compensation:** refers to an over-activation of the brain activity in old adults which helps acquiring certain level of performance and, at best, matches performance accuracy to that of young (Cabeza et al., 1997; Reuter-Lorenz et al., 2000; Cabeza et al., 2002). This hypothesis assumes that the older over-activated brain is "working harder" than the young brain to counteract for functional decline during cognition, and its effects have been frequently observed in brain hemispheric contralateral regions with a high predominance on prefrontal regions.

These two mechanisms are non-mutually exclusive. Indeed, and several explanatory models have been exposed to interpret brain activity increase in aging during cognitive performance:

*HAROLD*. Hemispheric asymmetry reduction in older adults (Cabeza, 2002). Based on fMRI studies, this model postulates the existence of a decreased prefrontal hemispheric lateralization of cognitive functions in old adults. Under this framework, the successful execution of a task which originally relies on just one hemisphere would require old adults to additionally recruit its counterpart (acquiring higher correct responses rate and reduced reaction times). This activation patterns have been explained to reflect either compensation and/or dedifferentiation and have been attributed to a reorganization of the brain networks in response to the neural changes accounted in aging.

*PASA*. Posterior-anterior shift in aging (Davis et al., 2008). First reported by Grady (1994), this model assumes a global shift in the brain function and postulates that under the same behavioral performance, old adults will show reduced occipital activation and increased prefrontal activation patterns than young adults. In this sense, prefrontal activity increase has been related with the utilization of cognitive strategies, which help to compensate brain posterior deficits and under-activation, for an improvement of the task performance.

*ELSA*. Early to late shift in aging (Dew et al., 2011). Based on behavioral and neuroimaging studies, this model postulates that "over the course of highly controlled

cognitive tasks, older adults shift from an early- to late-onset executive control strategy". That is, during performance of an executive control task which requires the maintenance of probe goals in the context of cues (Cue-Target continuous performance test), old adults fail to use cue information (showing reduced brain PFC activation) and wait to the target (showing increased brain PFC activation), suggesting that they shift from a proactive (mediated by the cue) to a reactive (mediated by the target) cognitive control strategy.

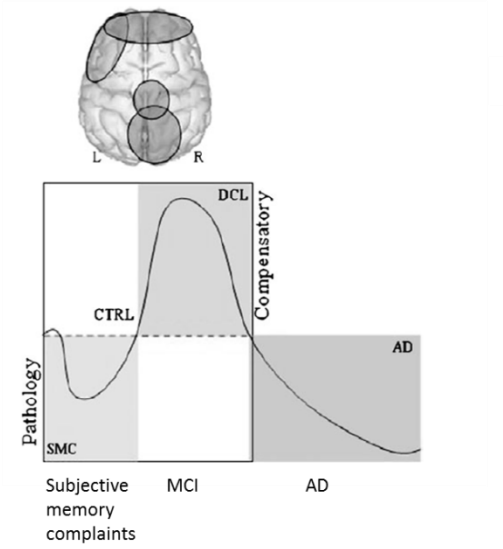
*CRUNCH*. Compensation Related Utilization of Neural Circuits Hypothesis (Reuter-Lorenz and Cappell, 2008). This model postulates that at low levels of cognitive load (when the task is easier) old adults recruit more neural resources and increase their brain activity to compensate for cognitive deficits. This over-activation leads adults acquiring equivalent levels of performance to that of young. Contrary, when the task difficulty increases, old adults reach a resource ceiling leading to brain under-activation and performance level drop in comparison with that of young.

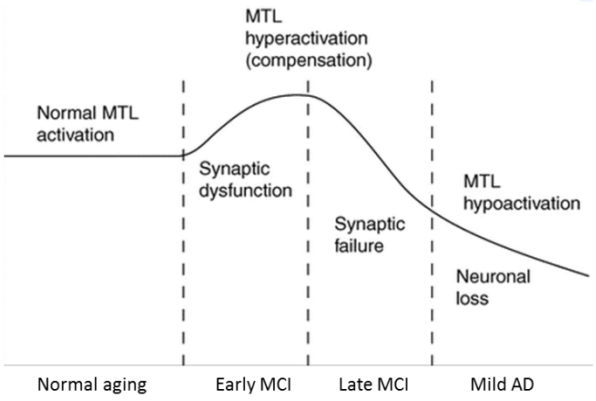
The abovementioned models show that reorganization capacity of the brain plays an important role in aging. Indeed, the plasticity and reorganization capacities of our brain allow us to counterbalance for brain alterations, even at initial/ mild pathological processes such as accounts in MCI (Castellanos et al., 2010; Grady, 2008).

In this line, accumulation of brain lesions as neurodegenerative diseases progress results in modulations of the functional brain activity and in consequence, in modulations on cognitive performance (Prvulovic et al., 2008). Evidence suggests that the process to AD is characterized by a dynamic shift from normal to hyper-activation with a posterior switch to hypo-activation as the disease progresses in the brain (see Dickerson and Sperling, 2008 and Sperling et al., 2010 for a review about brain activations in the continuum to AD). In this line, during the first phases of the AD disease, the brain preserves available resources to compensate for the underlying lesions. This results in additional effort (hyper-activation) of mildly affected brain areas and potentially, recruitment of alternative areas. All this together, seems to support compensation of the underlying pathology which helps slowing cognitive decline. However, advanced

stages of the disease and higher brain damage leads the brain to loss its plasticity capacity and causes brain activity and cognitive abilities reductions. Below two representational models of the brain modulation across the continuum to AD.

**Two representational models showing the brain activity modulations in the progression to Alzheimer's disease**




Source: Bajo et al., 2011; Pihlajamäki and Sperling, 2008

## 4. WORKING MEMORY AND INTERFERENCE

The term WM refers to the capacity of the brain to maintain, and when necessary manipulate, information during short periods of time when it is no longer present in the environment (Baddeley, 1986). In consequence, it plays an essential role in complex cognition, in processes such as language comprehension, learning, planning, reasoning or general fluid intelligence (Kane & Engle, 2002), and in the day living activities (i.e. reading or listening to news, doing the housework, mentally organizing the shopping list or calculating the monthly expenses).

WM can be understood as a capacity limited attentional control system which works on and coordinates the subprocesses required to select task-relevant information by limiting representations of task-irrelevant information, as is interference (Baddeley 1986; Sakai et al., 2002; Sakai 2003; Sakai and Passingham 2004; Miyake and Shah, 1999; D'Esposito & Postle, 1999; Sreenivasan and Jha 2007; Yoon et al. 2006). Four main processes have been proposed to underlie this system: 1) executive attention which focusses resources on task relevant information; 2) inhibition of task irrelevant information, 3) update and monitoring of contents and objectives of the ongoing task, and 4) switching between tasks or mental states. When these capacities are intact and task demands are not high enough, adequate coordination of these processes results in an optimal WM performance. However, alteration of these capacities, increase in task demands or the presence of potential interference stimuli, result in a depletion of performance and frequently, in forgetting of information.

Interfere stimuli can be classified in: Internal and External (Forster and Lavie, 2009; Clapp & Gazzaley, 2012). For the present work, we will focus on External stimuli due to its ecological significance. Two general categories of external interfering stimuli have been differentiated based on the cognitive demands: distraction and interruption.

- *Distraction* refers to task irrelevant stimuli which need to be ignored (e.g. ignoring a fly while studying), and its resolution relies on inhibitory abilities.

- *Interruption* refers to stimuli which demand additional processing as a secondary task (also considered multitasking, e.g. attending to a phone-call while cooking; Salvucci & Taatgen, 2008), and its resolution relies on task-switching abilities.

### 4.1. Working memory and interference in healthy aging

The inhibitory model proposed by Hasher & Zacks (1988) postulates that the ability to ignore or control distracting information underlies cognitive deficits in aging. That is, "older adults are less able to regulate their attention and they end up processing more distracting information than younger adults" resulting in difficulties to perform the task successfully (Healey, Campbell and Hasher, 2008).
Support for this hypothesis comes from literature showing age-related deficits in cognitive control processes including inhibitory control, switching attention between tasks and in the ability to regulate interference (Chao & Knight, 1997; Gazzaley et al., 2005; Sweeney et al., 2001; Crossley and Hiscock, 1992; Kramer et al., 1995; Clapp et al., 2012; Jonides et al., 2000 Darowski et al., 2008).

WM declines with age, and difficulties in WM have been observed to exacerbate in the presence of interference.
A strong behavioural and neuroimaging research line is nowadays being developed focusing on the study of the impact of interference (distraction and interruption) in WM maintenance in healthy aging (Clapp et al., 2011; Clapp & Gazzaley, 2012; Solesio et al., 2011, 2012). Results show that both interference stimuli consistently contribute to forgetting in aging and indicate that disruption of memory by distraction in aging is related to deficits in inhibitory control, and that disruption of memory in aging by interruption is related to deficits in shifting attention between two concurrent tasks.

Further, reduced ability to recruit brain prefrontal regions has explained difficulties to avoid interference.

These findings show that difficulties to control interference contribute to forgetting in healthy aging. So now, do MCI patients show difficulties to handle interference? Do they present inhibitory or task-switching deficits? Does interference contribute to forgetting in MCI?

### 4.2. Working memory in mild cognitive impairment

Evaluation of WM capacity in MCI and AD patients, through validated neuropsychological tests and through experimental paradigms, reveals that MCI patients show difficulties maintaining information in memory during short periods of time, and these difficulties increase when the task requires additional manipulation of information (see Huntley and Howard for a neuropsychological review of alterations in WM in the continuum to AD).

Clinical neuroimaging research aims to understand the brain mechanisms underlying memory abilities in MCI and AD patients. In this line, an fMRI study by Hamalainen et al., (2007) investigated encoding processes of associative picture-word pairs in MCI patients. Results revealed increased brain activation in posterior medial temporal regions when compared with healthy controls, which was linearly correlated to the atrophy of the anterior portion of the hippocampus in the group of patients. Similarly, in an encoding task with visual stimuli, the MCI subjects had higher activation in right parahippocampal gyrus compared to controls. Additionally, those patients that showed the greatest activation in this region had the greater cognitive decline within the following 2.5 years (Dickerson et al., 2004)

In a study by Kochan et al., (2010), brain activity patterns were also studied with fMRI during encoding but under several loads. Results showed that under low loads, MCI patients over-activated right anterior cingulate and precuneus regions, whereas under high memory load, they under-activated these areas and posterior cingulate-medial precuneus. In a similar study, they observed that greater deactivation patterns under

high memory load were related with functional decline, suggesting its possible relation with progression to dementia (Kochan et al., 2011).

An fMRI verbal WM study (Bokde et al., 2010) revealed over-activations in MCI patients during the encoding, retention and recognition phases of a WM task, when comparing with adult controls. Interestingly, the largest differences between groups were found during the delay over frontal and parietal brain regions. Both groups were matched in performance so it is forward that these brain activity patterns may represent compensatory mechanisms which allow overcoming the underlying brain pathology.

Using positron-emission tomography (PET), Grady et al., (2001) studied brain functional activity in AD patients during several retention periods of a delayed recognition memory task with faces. AD patients showed reduced memory performance with increasing delay periods. Furthermore, they showed functional disconnection between the prefrontal cortex and hippocampus, suggesting a reduction in the integrated activity within a distributed network including these two areas.

The group of Giannakopoulos in Switzerland has been interested in the study of oscillatory responses in MCI during WM tasks. For this purpose, they have studied EEG brain activity responses to n-back tasks under several loads, and they have also focused research on investigating brain activity patterns which could differentiate between stable and MCI patients likely to progress to AD. One of their results indicates that MCIs who later progress to AD show longer latencies of P200 and N200 components, reduced theta event-related synchronization after stimulus presentation and reduced event-related beta synchronization during the inter stimulus interval (Missonnier et al., 2006, 2007).

Moreover, the Sternberg paradigm has been largely utilized in MCI to study memory encoding and recognition processes. Based on this, one of the first approximations in MCI patients showed prefrontal over-activation under correct responses when comparing with controls (Heun et al., 2007).

The group of Maestú in Madrid has join forces in identifying memory brain magnetic features that characterize MCI. Up to now, they have worked under a modified version

of the Sternberg memory paradigm trying to understand brain memory recognition patterns that differentiate healthy and pathological aging. Significant results reveal that MCI patients are characterized by bilateral brain activity increase over the ventral pathway (Maestú et al., 2008), with additional brain activation in the dorsal pathway in those MCI patients who progress to AD (Maestú et al., 2011). Due to methodological advances, Bajo et al., (2010) interestingly have revealed higher interhemispheric synchronization between prefrontal and temporal MEG sensors and in posterior sensors, and reduced synchronization in fronto-posterior, left temporal and central sensors in MCI patients during successful memory recognition, when comparing with controls.

A study evaluating the brain oscillatory activity during the retention period of the Sternberg paradigm revealed that AD individuals showed reduced event-related desynchronization in the beta and was interpreted to represent WM dysfunction (Kurimoto et al., 2012). However, no differences were found between healthy controls and MCI patients, which could be explained by the characteristics of the samples and/or by the demands of the task, possibly being not sufficient difference between both groups.

These data indicate that MCI patients are mostly characterized by brain over-activations during memory tasks, which depend of the nature of the stimuli, complexity of the task and on the clinical status of the sample. Most of this research has been focused on the encoding and recognition phases of WM tasks without interference, whereas less attention has been focused on how MCIs maintain information in the absence and presence of interference.

### 4.3. Inhibition and task-switching in mild cognitive impairment

Difficulties in cognitive control abilities, including inhibition, task switching and interference resolution, have been accounted in MCI and AD patients.

An interesting review study by Amieva et al., (2004) analyzed the existent literature regarding inhibitory functioning in AD. They studied the effect of AD on the main paradigms to evaluate automatic inhibition: inhibition of return, retrieval induce

forgetting; and controlled inhibition: negative priming, go/no-go, stop signal task, Hayling task, trail making task, Stroop task and antisaccades tasks. Conclusions confirmed a direct impact of inhibition on the pathology with a greater impact of tasks requiring controlled inhibition than automatic inhibition. In agreement with these results, a recent neuropsychological study in which executive sub-domains were evaluated in MCI patients, Johns et al., (2012) observed that these patients show a particular impairment in inhibitory control. Belleville et al., (2007) provided empirical data regarding manipulation (measured by comparing immediate serial recall with alphabetical-order recall of words), divided attention (tested with the Brown-Peterson procedure) and inhibition (tested with the Hayling procedure) subcomponents of executive functions in both AD and MCI patients. The study concluded that the cognitive decline is accompanied by deficits in executive functioning and that impairment in attentional control occurs as the disease progresses.

Li et al., (2009) recorded with fMRI the brain activity during the execution of the Stroop task. Results revealed that MC patients increased their brain activity in the anterior cingulate, prefrontal, parietal and insula regions of the brain. Contrary, AD patients reduced their prefrontal brain activity. These results are in agreement with previous results showing distributed overactivations in MCI during the execution of the same task (Kaufmann et al., 2008).

Similarly, a study by Baddeley et al., (2001) examined the capacity of AD patients to focus attention in a simple and choice reaction time task, resist distraction in a visual search task and the capacity to divide attention between two concurrent tasks. Results revealed that patients are significantly impaired when irrelevant stimuli must be suppressed and when attention needs to be changed between two simultaneous tasks. In accordance with these results, a recent neuroimaging study by Clèment et al., (2012) divided MCI participants into two groups based on the Mattis Dementia Rating Scale (MDRS). Subjects performed a divided attention task while their brain activity was recorded with fMRI. Results showed reduced capacity for task-shifting in MCI compared with healthy elderly. Further, performance of high-cognition participants was associated with higher brain activation while low-cognition

participants did not show brain activation differences compared to controls suggesting that divided-attention abilities worsen as the pathology progresses.

The above revised literature indicates that memory is not the only cognitive process which is altered at early stages of the disease. However, the effect of cognitive control abilities on memory in MCI patients is not conclusive.

### 4.4. Interference in memory in mild cognitive impairment

An extensive research line from Cowan, Dewar and Della Sala's group have focused on the role of interference on long-term memory processes in cognitive aging (Della Sala et al., 2005; Dewar et al., 2009, 2012). Their findings reveal that memory consolidation in MCI is negatively affected by post learning non-specific interference. They argued that memory consolidation is enhanced by delays of "minimal-interference", that is, periods in which participants rest in a quiet room without performing any additional task. In a parallel manner, results from Californian verbal learning- like tests reflect that MCI patients are vulnerable to semantic interference and reveal its predictive value on conversion to dementia (Loewenstein et al., 2007; Rabin et al., 2009; Silva et al., 2012).

The effect of interference in WM, although not extensively, has also been accounted in MCI research. Belleville et al., (2007) used the Brown-Peterson procedure which involves maintenance of information in memory while performing an additional task. The outcome from this study revealed reduced memory accuracy while performing two concurrent tasks simultaneously in AD and MCI patients. Further, results correlated positively with global severity (assessed by the Mattis dementia rating scale, MDRS) suggesting that vulnerability to interference in memory increases as function of the severity of the disease. Similarly, a study by Alescio-Lautier et al., (2007) aimed to observe difficulties in dividing attention between interference and memory probe stimuli in MCI and AD patients.

Interestingly, Deiber et al., (2011) explored electroencephalographic (EEG) activity patterns in single-domain amnesic (sd-aMCI) and multidomain amnesic MCI during a

WM with distraction task. Results showed reduced ability to suppress irrelevant stimuli at encoding (revealed through reduced alpha synchronization) in both MCI groups when comparing with controls, with greater difficulties in the md-a MCIs. However, at the recognition phase, md-aMCI patients showed significant reduced recognition effect (revealed by the N250r component) than healthy controls, suggesting specific alteration of recognition processes in md-aMCI patients.

Overall, evidence reveals that MCI is characterized by deficits in WM and cognitive control abilities, including interference resolution. However, how cognitive controls deficits affect WM in MCI is not conclusive. Furthermore, studies which jointly examine potential different effects of distraction and interruption in WM in MCI patients have not been developed yet. Such a study will offer new perspectives about the causes that contribute to forgetting in MCI.

## 5. MAGNETOENCEPHALOGRAPHY

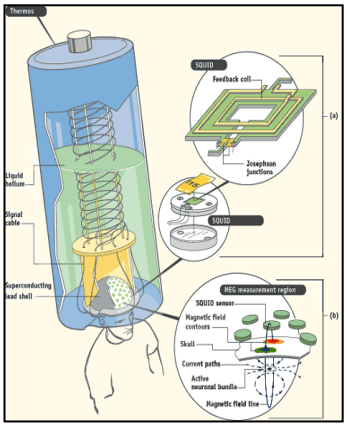
Magnetoencephalography (MEG) is a relatively new, non-invasive neurophysiological technique which captures the sum of very small magnetic fields (on the order of femtoTesla, fT) generated by the electric currents of our brain.

The main characteristic of the MEG is the high time resolution information that offers (milliseconds) about the ongoing brain activity. This is of extremely importance when studying cognition, since cognitive processes simulate a temporally high synchronized orchestra which necessitates of an adequate integration and coordination of the instruments (cell assemblies) for its correct functioning.

Every electrical signal generates a perpendicular magnetic field, which in the case of the brain, is generated by the neurons. In baseline, a neuron contains a charge difference between the inside and outside of its membrane (called: to be polarized) which is caused by differences in the concentration of ions. Whenever a neuron is excited, the permeability of the neuron changes, allows ionic circulation through it and in consequence, the polarization of the cell changes. This ionic circulation produces an intracellular current, which in turn produces an extracellular current. Neuronal activity can be distinguished in presynaptic and postsynaptic. The first refers to the depolarization of the cell which generates an electrical signal (called action potential) which is propagated along the axon of the neuron. This electric signal decays rapidly over time (1ms). The second can be distinguished in excitatory and inhibitory potentials which are generated in the postsynaptic dendrites and which propagate along the axon of the cell. Excitatory potentials refer to a depolarization of the neuron caused by arrival of positive ions from the action potential to the synapsis. Inhibitory potentials refer to a hyperpolarization of the cell caused by the arrival of negative ions.

These postsynaptic signals last for a set of ten milliseconds and are what MEG detects (Carretié, 2001; Maestú et al., 2007).

However, the detection of the magnetic fields from outside the scalp depends on the morphology, orientation and on the number of neurons simultaneously activated. Thereby, the MEG signal is the result of the synchronous activation of parallel distributed 30.000 (10x5) pyramidal neurons on the sulci (due to the orientation of the dendrites which are perpendicular to the scalp) of layers III and V of the brain (Hämäläinen & Hari 2000; Maestú et al. 2008).




The small magnitude of the magnetic fields from outside the scalp (~10-100 fT), have led to the development of high sensible detectors of magnetic field variations: SQUID (Superconducting Quantum Interference Device; composed commonly by magnetometers and gradiometers), which need extremely low temperatures to maintain its superconductivity features. For that purpose, the SQUID system is immersed on a Dewar filled with liquid helium at -269$^0$ of temperature. Further, the MEG system is commonly located inside an isolated camera that avoids external magnetic noise from the environment.

This study was performed with an Elekta Neuromag system, which combines two types of SQUID-based sensors: 102 magnetometers and 204 planar gradiometers. Planar gradiometers measure the field gradient, using two adjacent coils and are mainly sensitive to superficial sources, while magnetometers detect sources within a broader spatial range. For this reason, magnetometers were used for this sensor space analysis

## 5.1. Brain oscillations

Electroencephalographic and magnetoencephalographic rhythms are defined as regularly recurring waveforms of similar shape and duration. The precise timing of neurons, results in oscillatory waveforms, that depending on time, can be characterized based on their phase (position of the oscillation in a time point), amplitude (maximal or minimal position of the wave during a period) and frequency (the number of repetitions of an oscillation during certain time). Nowadays, one of the most adequate methodologies to study the brain oscillatory activity is the one that characterizes its spectral features. The classical frequency analyses are based on the Fourier transform, which assumes a stable frequency spectrum across time. However, the oscillatory activity of our brain is not stationary, and its analysis requires the characterization of these frequencies over time (Buzsáki & Draguhn, 2004), as offered by the so called time-frequency analysis.

In 1929, Hans Berger described with EEG the first brain rhythm of about 10Hz which was named the “alpha rhythm”. Since then, low and high frequency rhythms have been observed, and have been traditionally divided in five main frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz) and gamma (>30 Hz). Brain functions are represented by the dynamical synchronization and desynchronization of the oscillatory neural activity of our brain (Varela et al., 2001; Buzsáki, 2004). In this sense, cognitive processes have been classically associated with specific frequency bands.

Delta frequency band is easily observed during sleep, and an increase of its amplitude/power is associated with pathological state on the brain. Theta waves are mainly associated with memory processes. Alpha rhythm is observable during wakeful relaxation during eyes close, and is blocked when eyes open. Additionally, has been recently related with inhibitory process as well as with memory processes. Beta waves have been largely observed during motor responses. Gamma activity has been related with eye saccadic movements, attention and information processing.

Active maintenance of sensory information is reflected by the sustained synchronous activity of local and distributed cell assemblies in the brain (Fuster and Alexander, 1971; Goldman-Rakic, 1990; Miller et al., 1996; Haxby et al., 2000; Varela et al., 2001; Wang et al., 2011). In this line, any external stimulus, such as interference, holds the potential to "break" or sum to the ongoing brain activity, reduce memory recall abilities and thus, facilitate forgetting of information.

The precise timing of neurons, results in oscillatory activity with an essential role of theta, alpha and gamma frequency bands in memory retention processes (Sauseng et al., 2010; Axmacher et al., 2008; Fuster, 2009). In this line, due to the relevant role of the oscillatory activity in functional communication, deviations from normal patterns are good candidates to study brain-related pathologies (Schnitzler and Gross, 2005).

The MCI literature has largely evidenced a slowing down of the frequency spectrum in this population, showing decreased activity in high frequencies (gamma) and increased activity in the low frequencies (delta, theta). Interestingly, values in the delta, theta and alpha frequency ranges have been correlated with hippocampal atrophy and cognitive decline in MCI patients during periods of resting state with eyes closed (Fernández et al., 2003, Moreti et al., 2009a, 2011; Grunwald et al., 2007, 2009; Babiloni).

However, how the brain oscillatory activity is modulated during WM retention processes in MCI has not been characterized yet. Studying the neural activity patterns of MCI patients during WM retention periods will offer knowledge about the mechanisms underlying memory capacity and forgetting in this pathology.

# Justification of the study

The above revised literature shows that interference depletes WM retention abilities and facilitates forgetting of the information held in memory. These difficulties have been related with alterations in cognitive control capacities (specifically in inhibition and task-switching abilities), which get evident in the process of normal and pathological aging.

MCI population, in addition to the common symptoms regarding episodic memory loss, is characterized by difficulties to maintain and manipulate information during short periods of time, and by difficulties to control attention between irrelevant stimuli and between two concurrent tasks. Thus, they are also characterized by difficulties to handle interference. However, up to now, the relation between cognitive control and WM has not been studied extensively in MCI patients. Furthermore, the potential differential contribution of distraction and interruption to WM forgetting in this population has not been studied yet.

Based on this, the motivation of first experiment of the present Thesis was to evaluate the relation between cognitive control and WM retention abilities in MCI. For that aim, a visual delayed-recognition WM paradigm was designed based on three main conditions: the first involved a delayed-recognition WM condition without any interference, the second included a distraction stimulus during the WM delay period, and the third included an interruption during the WM delay period. Each condition included both one and two memory loads. Altogether, this experiment will indicate the effects of each interruption stimulus and memory load on WM retention in MCI patients, and will serve to select the most appropriate design for the third experiment.

Functional neuroimaging studies commonly reveal memory-related over-activations in several regions of the brain of MCI patients when matching performance of controls. However, most of the studies are focused on encoding and retrieval phases of memory tasks, and there is no knowledge about the mechanisms underlying memory maintenance in MCI patients. Due to the role of the oscillatory activity of our brain on cognitive functions, the motivation of the second experiment was to study the brain oscillatory patterns supporting WM retention in MCI patients. For that aim, the delayed-recognition WM condition without interference form the first experiment was adapted for an MEG study. This experiment will allow us to study how, in the presence of objective memory deficits, the brain activity of MCI patients is modulated to successfully maintain information in memory. Additionally, would serve as the basis to understand the brain mechanisms accounting in the third experiment.

The sustained activity during memory retention periods is depleted in the presence of interference. Thus, studying the mechanisms underlying successful and unsuccessful WM accuracy in MCI patients would allow understanding the mechanisms responsible for WM forgetting in this population. The first experiment showed that interruption condition was the one causing higher rates of forgetting in MCI patients when comparing with controls. Additionally, the experiment showed that one memory load was sufficient to reveal WM depletion in this population. Based on this, the third experiment included two experimental conditions: one included the delayed-recognition WM condition without interference, and the second included delayed-recognition WM with interruption condition from the first experiment. The experimental paradigm was adapted for the MEG study. Studying correctly and incorrectly maintained periods will allow us disentangling the brain activity patterns underlying WM forgetting by interruption.

Altogether, the three experiments will offer a new perspective about the brain oscillatory patterns underlying WM forgetting in MCI patients.

# CHAPTER 2. Experiment I

## Interference modulates working memory in mild cognitive impairment

# 1. AIMS AND HYPOTHESIS

The main objectives of the first study were to study how WM maintenance is modulated by interference (distraction and interruption) in MCI and healthy controls, and the impact of WM load under high and low cognitive demands (no interference, distraction and interruption conditions) in these populations. This study will provide evidence about potential effects of interference on WM in MCI, and will help in the design of the third experiment.

In this experiment were expected higher WM forgetting rates by means of interruption, in comparison with distraction. We hypothesized that this reduction in accuracy would be more pronounced in the MCI than in the control groups, and that memory load would reduce performance in all of the conditions, with a more pronounced impact in the MCI participants.

# 2. METHODS

## 2.1. Participants

A total of 40 volunteers were included in the study. All of the participants were over 65 years of age. The participants were divided into two groups based on their clinical profiles (MCI patients and healthy adults). The groups were matched for age and educational level. The MCI group was recruited from the Hospital Clínico San Carlos of Madrid. The healthy control group was recruited from the Seniors Centre of the district of Chamartín, Madrid (see Table 1 for demographic characteristics and neuropsychological data).

All of the participants were screened using the following standardised diagnostic instruments: the Spanish version of the Mini Mental State Examination (MMSE; Lobo et al., 1979), the Global Deterioration Scale (GDS; Reisberg, 1982), the Functional assessment questionnaire (FAQ; Pfeffer, 1982), the Geriatric Depression Scale (GDS-15; Yesavage et al., 1982), the Hachinski Ischemic Score (HIS; Rosen et al., 1980), the questionnaire for Instrumental Activities of Daily Living (IADL; Lawton and Brodie,

1969), and the Functional Assessment Staging (FAST; Auer and Reisberg, 1997). The inclusion criteria included the absence of significant cerebral-vascular disease (i.e., modified Hachinski score ≤ 4) or depressive symptomatology (i.e., GDS-15 score < 6). The participants were not using drugs that could affect cognitive performance and were free of significant medical, neurologic and/or psychiatric diseases (other than MCI).

MCI diagnosis was established according to the Petersen (2004) criteria. Accordingly, MCI patients should fulfil the following requirements: (1) memory complaint, persisting for at least a 6 month duration and corroborated by an informant; (2) abnormal memory function, documented by delayed recall of one paragraph from the Logical Memory II subtest of the Wechsler Memory Scale-Revised (cut-off scores: ≤ 16 for ≥16 years of education; ≤ 8 for ≥8–15 years of education); (3) normal general cognitive function, as determined by a Mini-Mental State Examination (MMSE) score greater than or equal to 24; (4) total absence or minimal impairment in activities of daily living (ADLs) as revealed by the Lawton scale, determined by a clinical interview with the patient and informant; and (5) absence of dementia according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria as judged by an experienced clinician (McKhann et al., 1984). MCIs did not fulfil the diagnostic criteria for dementia (i.e., all were classified at stage 3 of the GDS).

Patients and controls received an exhaustive neuropsychological assessment to establish their performance level in multiple cognitive domains. The assessment included the following: Clock Drawing Test (Agrell and Dehlin, 1988), Direct and Inverse Digit Spam Tests (Wechsler Memory Scale-Revised, WMS-III; Wechsler, 1987), Immediate and Delayed Recall (WMS-III; Wechsler, 1987), Phonemic and Semantic Fluency (Controlled Oral Word Association Test, COWAT, Benton and Hamsher, 1989), Ideomotor Praxis of Barcelona Test (Peña- Casanova, 1990), Rule Shift Cards (BADS; Norris and Tate, 2000), Visual Object and Space Perception Test (VOSP; Warrington, 1991), Boston Naming Test (BNT; Kaplan et al., 1983) and Trail Making Test A and B (TMTA and TMTB; Reitan, 1958).

According to their clinical and neuropsychological profiles, the patients were diagnosed as amnesic-multidomain MCI showing a memory deficit and various degrees of impairment in cognitive domains such as language and/or executive functions (Petersen, 2004).

All of the participants or their legal representatives signed informed consent that explained the technical and ethical considerations of the investigation. The study was approved by the local ethics committee.

## 2.2. Stimuli

The stimuli used in the experiment consisted of neutral, anonymous male and female faces across a large age range. The hair and ears were removed digitally to avoid non-face-specific cues. The experiment was computerised through E-prime1.2 software (Psychology Software Tools, Inc.).

## 2.3. Experimental paradigm

The participants performed a delayed recognition WM paradigm with three interference conditions: no interference (NI), distraction (DIS) and interruption (INT) under two memory loads (1 and 2 items to memorise) (see Figure 1 for a representation of the paradigm). All of the conditions consisted of three main phases: encoding, maintenance and recognition. Thus, each participant performed 6 conditions (load1: NI1, DIS1, INT1; load2: NI2, DIS2, INT2). Each condition was presented in a block, a design which was revealed to be necessary because mixed versions in a pilot study caused floor performances. Furthermore, research in aging populations has traditionally utilised this type of design. The blocks consisted of 32 randomly presented trials, resulting in a total of 192 trials per participant. The block presentation order was counterbalanced across subjects.

Before each block, instructions regarding the upcoming task were given to the participants, after which a practice session was conducted to ensure adequate

understanding. In the encoding phase, a face (one or two, depending on the memory load) was displayed for a 1000 ms period and the participants were instructed to encode it. In the maintenance period, the participants were instructed to keep the encoded face (or faces) in mind for a 4000 ms delay period. This instruction varied between the conditions, depending on the presence or not of a distraction or interruption stimulus. In the recognition phase, a single face was displayed for 1000 ms, and the participants were instructed to make a match/non-match button press as rapidly as possible, without sacrificing accuracy, to indicate if the face was the same as the one presented in the encoding phase (or if it was one of the two faces presented in the encoding phase, in the case of the load2 conditions). To ensure that all of the participants had enough time to respond, a response slide ("no-yes") was displayed after the recognition phase and maintained until the participant made the button press. This response slide was followed by the instruction "next" for 500 ms, which indicated the step to the next trial. Both the encoding and retrieval phases were preceded by the instructions "memorise" and "compare" for 500 ms each, respectively, to ensure adequate orientation within each phase of the task. In the NI condition, a fixation cross was displayed in the centre of the screen for the 4000 ms of maintenance, and the participants were instructed to keep the encoded face (or faces) in mind during this period. In the DIS condition, a face stimulus was added as a distractor after the encoding phase for 1000 ms after the first 1500 ms of the maintenance period. The participants were instructed to ignore the distractor while maintaining the encoded face/s. The INT condition had an added face stimulus as an interruptor after the encoding phase, which was displayed for 1000 ms after the first 1500 ms of the maintenance period. The participants were instructed to make a button press if the interruption face was judged to be over 60 years of age while maintaining the encoded face. The interrupting face was presented between two question marks, indicating the additional requirement to process and respond to the stimulus. Twenty-five per cent of the interruption faces were aged over 60.

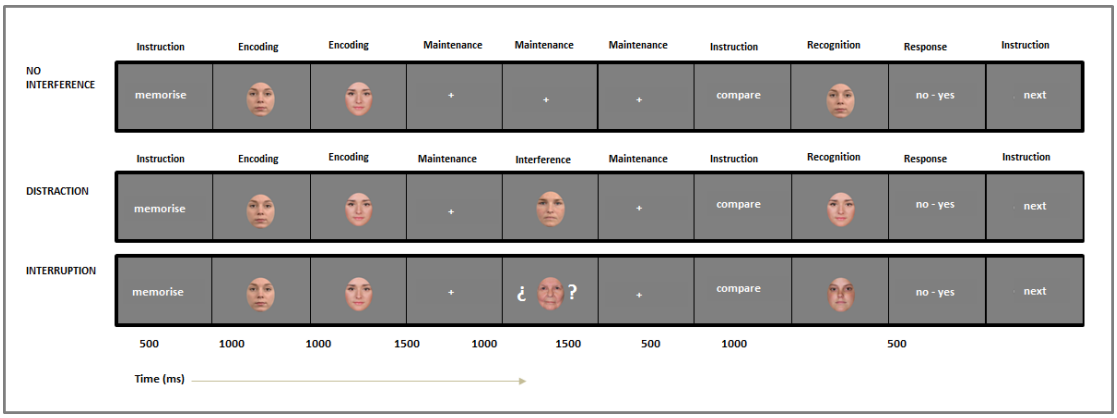



Figure 1. Representation of the experimental paradigm. The experimental paradigm consisted of three conditions: No Interference, Distraction and Interruption. All of the conditions were structured in three main phases: encoding, maintenance and recognition (see *Experimental paradigm* section for further explanation). Under load1, one face was presented in the encoding phase, whereas under load2, two faces were presented in the encoding phase.

## 2.4. Statistical analysis

To analyse the neuropsychological test scores between the groups, independent sample t-tests were performed.

Analysis of the delayed-recognition paradigm performance was based on correct responses for each condition, load and group. RTs greater than two seconds, and their respective accuracy scores, were discarded from the analysis. To statistically evaluate accuracy and RT across conditions and loads, and within and between groups, a three-way repeated measures ANOVA was performed using within-group factors of condition (NI, DIS and INT) and memory load (load1 and load2) and a between-group factor of diagnosis (control group and MCI group). All significant interactions were evaluated. The resulting p values were corrected using the Bonferroni correction procedure.

To further clarify the differential impact of interference stimuli on memory, accuracy in both of the interference conditions was normalised to the performance of the no-interference condition. Based on the condition x diagnosis interaction obtained (see below), accuracy under both loads (load1 and load2) in each condition was added and treated as one score (i.e., accuracy of NI=NI1+NI2). For that purpose, the effect of distraction and interruption was calculated for each group of participants using Z

scores: *Effect of Interference= mean[(I-X)/SD]*, where *I* is the accuracy during DIS or INT for each participant and *X* and *SD* are the mean values and standard deviation of the group for NI. Once the Z scores were calculated, independent sample t-tests were performed for each score to examine if the effect of interference would differentially impact performance between the groups.

# 3. RESULTS

## 3.1. Neuropsychological results

Analysis of the neuropsychological assessment between the groups revealed significantly reduced accuracy in the MCI participants compared to the controls in the following tests: MMSE, CDT-Copy, DD, ID, Imm. Rec. and Del. Rec., FAS-F, FAS-S, Cards-BADS and BNT (all comparisons $p<0.05$). Due to the potential contribution of age or educational level to differences in performance, it is important to take into account any possible differences in these attributes between the groups. The demographic data in the present study showed no significant differences between the groups regarding this issue (all comparisons $p>0.05$). We therefore are able to assume that the obtained results were not influenced by either of these variables.

| DEMOGRAPHY AND NEUROPSYCHOLOGY | | |
|---|---|---|
| | CNT | MCI |
| **Age** | 70.5(3) | 73.6(3.5) |
| **Educ. Level** | 3.9(1) | 3(1.2) |
| **Gender** | 12F 8M | 9F 11M |
| **MMSE** | 29.4(0.6) | 28.2(1.7) * |
| **GDS** | 1(0) | 3(0) |
| **CDT-Order** | 7(0) | 6.5(1) * |
| **CDT-Copy** | 7(0) | 6.3(0.8) * |
| **DD** | 8.9(2.7) | 6.4(1.5) * |
| **ID** | 6(2) | 4.7(1.1) * |
| **Immed Rec** | 40.2(8) | 20.8(11) * |
| **Delayed Rec** | 26.5(7.9) | 9.5(8.7) * |
| **FAS-F** | 15.2(3.9) | 10.2(4) * |
| **FAS-S** | 17.3(3.7) | 12.2(4) * |
| **Ideo. Praxis** | 7.9(0.2) | 7.6(0.7) |
| **Cards-BADS** | 3.3(1) | 2.3(1.5) * |
| **TMT-A** | 23.7(0.9) | 24(0) |
| **TMT-B** | 21.1(3.3) | 20.5(4.5) |
| **BNT** | 55.8(3.9) | 51.2(7.4) * |
| **VOSP** | 9.2(2.8) | 9(3.1) |
| **FAQ** | 0.06(0.2) | 0.8(1.5) |
| **GDS-15** | 2.2(3.9) | 2.1(2.4) |

Table1. Demography and neuropsychology. The demographic data and neuropsychological results are shown (mean scores and standard deviations in brackets for each group). Asterisks (*) indicate significance with p below 0.05 between the groups.

### 3.2. Experimental tasks performance

The performance results from the experimental tasks are shown in Figure 2.

#### 3.2.1. Accuracy

The analysis resulted in a main effect of diagnosis [$F(1,38)=24.96$; $p<0.001$], with lower performance in MCI versus control individuals; condition [$F(1,38)=116.42$; $p<0.001$], where the participants showed decreased accuracy according to the demands of the interference conditions; and load [$F(1,38)=194.28$; $p<0.001$], where the participants displayed reduced accuracy as a function of the increase in memory load. Additionally, there were significant 2-way interactions of condition x diagnosis [$F(1,38)=18.66$; $p<0.001$] and condition x load [$F(1,38)=26.53$; $p<0.001$].

An evaluation of the condition x diagnosis interaction showed reduced accuracy across the three conditions in the MCI individuals compared with the healthy controls (NI, DIS and INT, $p<0.01$). The memory of the MCI patients was affected by both interference conditions (DIS and INT in comparison with NI, $p<0.01$). However, accuracy in the INT condition was lower than in the DIS condition ($p<0.01$). In the case of the control group, INT revealed lower accuracy than the NI and DIS conditions ($p<0.01$), without a significant difference between the DIS and NI conditions ($p>0.05$). An evaluation of the condition x load interaction showed that accuracy during each condition was lower under load2 than under load1 (when evaluating NI, DIS and INT between loads; all comparisons $p<0.001$). Furthermore, the participants overall progressively reduced their accuracy according to the demands of the interference stimuli (reduced progressive accuracy across NI, DIS and INT conditions) when the memory load was

low (load1; all comparisons between conditions, p<0.001). However, under higher memory load (load2), accuracy reduction was only observed in the INT condition when compared to DIS (p<0.001) (see Figure 2, left).

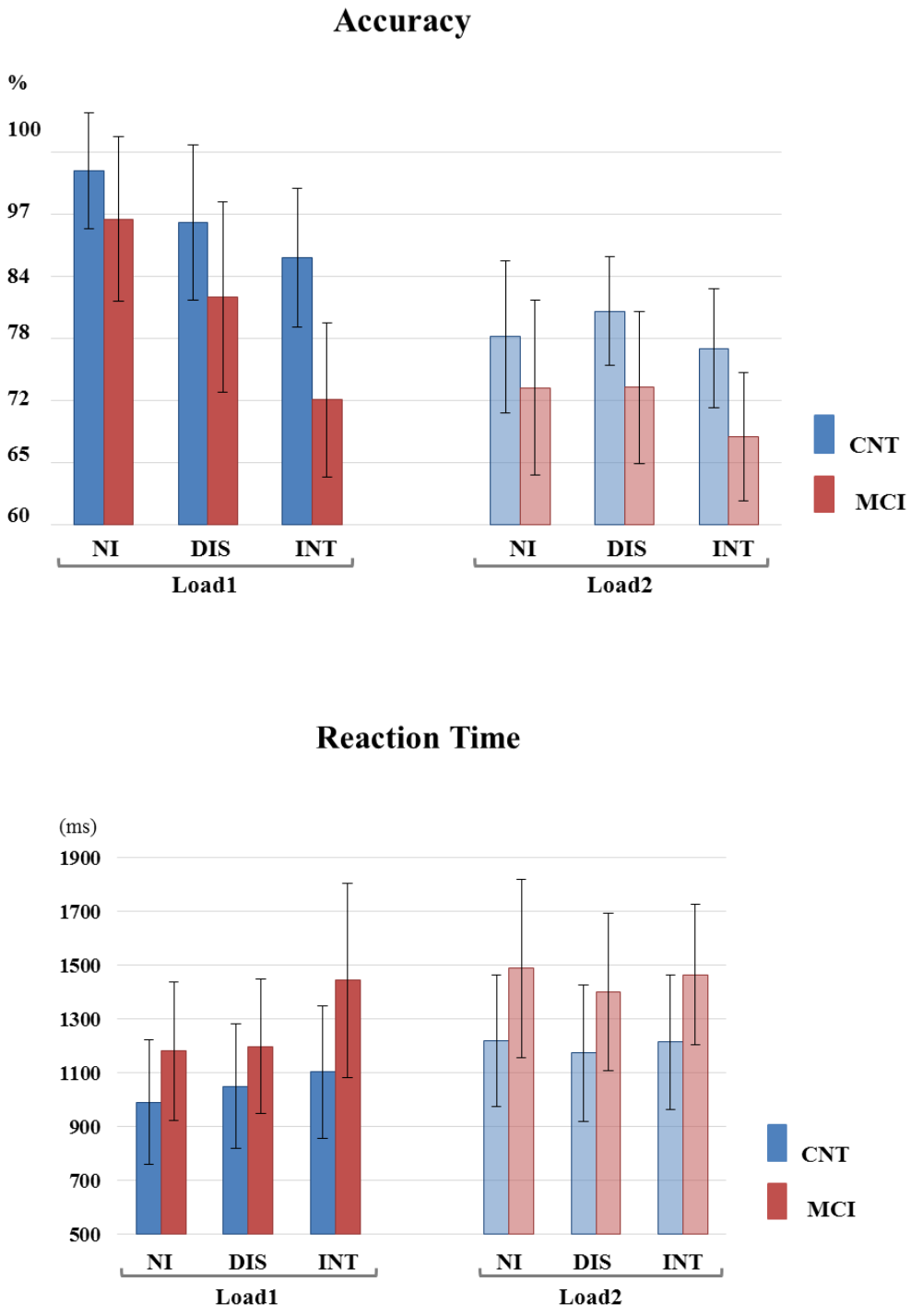



Figure 2. Performance, accuracy and reaction times are shown on the left and right, respectively. The performance of the controls, CNT, is shown in the blue bars; the performance

of the MCIs is shown in the red bars. Load1 is represented by solid colours. Load2 is represented by light colours. The X-axis represents the experimental conditions (no interference, NI; distraction, DIS; interruption, INT). The Y-axis represents on the left: percentage (%) of correct responses; on the right: reaction time in milliseconds, ms. The error bars represent standard deviations from the mean. See text for significances.

**Effect of interference on accuracy**

A between group analysis of the effect of interference on accuracy revealed a tendency to a higher effect of interruption (*Effect Interruption*) on the MCI participants compared to the healthy controls [t(38)=1.96, p=0.056]. However, no differences were found between groups regarding the effect of distraction [t(38)=0.1, p>0.05]. See Figure 3.

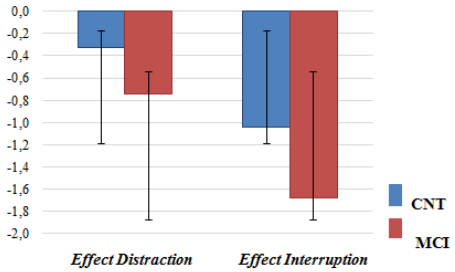



Figure 3. Effect of interference on accuracy reveals that the MCI participants are more affected than the controls, CNT, by the interruption condition. The X-axis represents the effect of the conditions. The Y-axis shows the value of the effect (see *Methods* for calculation). The effects for the CNTs are shown by the blue bars, and those of the MCIs are shown in red. The error bars represent standard deviations from the mean.

### 3.2.2. Reaction time

The analysis resulted in a main effect of diagnosis [F(1,38)=12.87; p=0.001], revealing larger RTs for the MCI patients compared to the control participants; condition [F(1,38)=8.67; p<0.01], where the participants had larger RTs in the INT condition; and load [F(1,38)=28.44; p<0.001], where the participants showed larger RTs as a function of memory load. Additionally, there was a significant 2-way interaction of condition x load [F(1,38)=8.81; p<0.01].

An evaluation of this interaction showed that increased memory load enlarged the RTs of the participants in the NI and DIS conditions (p<0.01). However, the RTs were similar

between the INT1 and INT2 conditions ($p>0.05$). Furthermore, the participants were slower during the INT condition under low memory load (when comparing INT with NI and DIS; $p<0.01$), whereas under high memory load (load2), no differences in processing speed were observed between the conditions ($p>0.05$) (see Figure 2, right).

## 4. DISCUSSION

A deficit in episodic memory has traditionally been the quintessential feature of the continuum to AD. Indeed, it is one of the inclusion criteria for the diagnosis (Petersen, 2004; Dubois et al., 2011). However, evidence suggests that episodic memory impairment is not the only cognitive deficit that characterises MCI; executive deficits have been described as well (Baddeley et al., 1986; Collette et al., 1999; Amieva et al., 2004b; Belleville et al., 2007; Saunders & Summers, 2010; Gagnon & Belleville, 2011; Clément et al., 2012; Johns et al., 2012). In the present study, we tested the effect of two types of interference, distraction and interruption, during the maintenance of different amount of information in WM, load1 and load2, in MCI and healthy control volunteers. The main result of our study revealed reduced memory accuracy in the MCI participants, when compared with the controls, showing a progressive reduction in accuracy as the demands of the conditions increased (from NI to DIS and INT). Furthermore, the presence of interruption was the most devastating for memory, especially in the MCI patients. Additionally, all of the participants showed reduced performance (lower accuracy and slower RTs) in all of the conditions where the memory load increased, and a greater impact of interruption compared to distraction was observed under both memory loads.

### No interference

As revealed by the current experimental design, MCIs showed more difficulties than the controls in maintaining information in memory in the absence of an interference stimulus (NI). These data are in agreement with previous findings establishing these difficulties as the central hallmarks of MCI and AD (Welsh, Butters, Hughes, Mohs & Heyman 1992; Hulme, Lee & Brown, 1993; Collette, Van der Linden, Bechet & Salmon,

1999; Petersen et al., 1999; Caza & Belleville, 2008; Huntley & Howard, 2010; Maki, Yoshida & Yamaguchi, 2010; see Huntley & Howard, 2010 for a neuropsychological review). Furthermore, these difficulties are augmented by memory load, which was observed in all of the participants. In agreement with previous literature (Alescio-Lautier et al., 2007; Bird et al., 2010; Gagnon & Belleville, 2011; Kessels et al., 2010; Bennett et al., 2013), these results confirm the existence of difficulty maintaining information during short delays in MCI and indicate that these alterations tend to increase when the amount of information to be retained increases. However, the fact that performance on NI was higher than in the other two experimental conditions, especially in the MCIs, indicates that the effect of interference must be explored in detail. Future behavioural and neuroimaging studies evaluating the maintenance of information under multiple loads in MCI would be interesting to extend our knowledge regarding the neurophysiological mechanisms that underlie forgetting.

With respect to RTs, the MCI participants showed an overall slower response when responding to the tasks compared to the healthy volunteers. The "processing speed hypothesis" attributes performance deficits to a decline in processing speed in healthy and pathological aging (Salthouse, 1996; Sylvain-Roy, Bherer & Belleville, 2010). Nevertheless, considering that the RTs in the current results were all related to accurate responses, the time-cost trade-off appears to be more attributable to WM demands than to deficits in processing speed. The same interpretations account for the effects in the interference conditions.

**Distraction**

Handling distraction during memory processes requires WM and inhibitory control abilities, which allow maintaining and updating, and the voluntarily suppression of irrelevant information. Thus, alteration in any of these processes causes higher representation of the to-be-ignored material in WM, which, if combined with deficits in suppression, results in forgetting the relevant information (Hedden & Park, 2001). Based on this, our findings revealing reduced memory accuracy, in all participants,

when distraction was present under low load demands suggest possible relation between inhibitory difficulties and memory decline in aging.

The aging literature reveals that when AD-related symptoms become visible, deficits in inhibition and in resolving interference emerge (Collette et al., 1999, 2009; Amieva et al., 2004b; Belleville et al., 2006; Wylie et al., 2007; Bélanger & Belleville 2009). These findings appear to explain our results (regarding the condition x diagnosis interaction), which show that the memory accuracy of the MCI participants was negatively impacted by distraction and significantly reduced when compared with the matching volunteers. Along these lines, impairments in the control of actively suppressing irrelevant stimuli, in addition to primary episodic memory deficits, could better explain the high rate of forgetting showed in daily living activities by the MCI population.

A recent study exploring this hypothesis examined the electroencephalographic activity of MCIs during the encoding and retrieval phases of a WM with distraction task (Deiber et al., 2011). The experimental design included two faces and two letter stimuli presented in an interspersed manner, which had to be encoded or suppressed depending on the instructions before each trial. The results revealed altered suppression of brain activity for distracting stimuli in multi-domain MCI patients compared to healthy controls. Thus, the authors concluded that difficulty in suppressing/inhibiting irrelevant stimuli plays a key role in short-term memory forgetting in MCI patients. In agreement with the current findings, the previous results indicated the existence of WM deficits in MCI pathology, specifically, a reduced capacity for patients to maintain information in memory when handling low demand interference. In line with the abovementioned studies and our expectations, we assume that memory deficits in MCI individuals are influenced by the presence of irrelevant information, most likely due to difficulties in inhibitory processing.

Contrary to our expectations, the condition x load interaction revealed that when the participants were asked to maintain two items in memory, the performance (accuracy and RT) was similar in the absence of any interference and when distraction needed to be suppressed. These results appear counterintuitive because a higher impact of distraction under higher memory load demands would be expected. However, there is

evidence suggesting the existence of different consequences on distractor processing related to the WM load type (Kim et al., 2005; Park et al., 2007). Along these lines, attentional resources have been shown to be easily depleted by demanding perceptual tasks, leaving limited attention for distraction (Lavie et al., 2004). Furthermore, studies examining the impact of distraction under various WM loads show reduced distractor processing under a high load in both young and healthy elderly individuals (Rose et al., 2004; Gazzaley et al., 2007). Consequently, a tentative explanation would be that the high maintenance demand of two items in memory prevents distraction from entering into WM, resulting in a reduced requirement for inhibitory processes, and eliciting an equivalent level of performance in DIS2 and NI2. Therefore, the consumption of resources provoked by a high WM load would hinder the processing of additional information and would result in a sole focus on the to-be-maintained information. An additional explanation for the present findings could also rely on the fact that participants could increase their efforts while performing a highly demanding condition, such as DIS2, in comparison with the low demanding conditions. These data indicate the importance of the amount of information to be held in memory when studying the influence of interference. Regardless, further research analysing the relation between distraction and memory maintenance under multiple WM loads in aging would be helpful to better clarify these findings.

Overall, these data suggest that MCI patients are more vulnerable to distracting stimuli than healthy controls and that these difficulties play an important role in the well-known memory deficits of MCI. Additionally, we can conclude that when the amount of information to be retained increases, the impact of distraction on memory is more diffuse in aging and should be more thoroughly investigated.

**Interruption**

Handling interruption during WM maintenance has been classified as a process requiring multitasking (Sakai et al., 2002a, b; Clapp et al., 2010), and alterations in this process have been observed in healthy adults and MCI and AD individuals (Albert et al.,

2001; Baddeley et al., 2001; Belleville et al., 2008b; Borkowska et al., 2009; Lonie et al., 2009; Festa et al., 2010; Sinai et al., 2010; Clapp et al., 2011; Clément et al., 2012).

Our results and hypothesis agree with these findings and show that both groups of participants had reduced accuracy and increased RTs when interruption was present during memory maintenance. Interestingly, the condition x diagnosis interaction revealed that memory disruption by interruption was greater in the MCI patients than in the controls. This finding is in line with the high *effect of interruption* observed in the MCI group. In a similar manner to this finding, a study performed by Belleville et al., (2007) assessed attentional control processes in MCI using three experimental tasks. The most significant results were found with a modified version of the Brown-Peterson procedure (Morris, 1986). In this task, information is maintained over short delays while an additional task, completing addition, is performed. MCI participants showed difficulty maintaining information in memory in the presence of the secondary task. Furthermore, memory accuracy was related to the overall severity of the patients, suggesting a gradual decline between memory and interference resolution capacities in the continuum to AD. In a similar manner, Alescio-Lautier (2007) evaluated the memory recognition abilities of AD and MCI patients during delayed periods that were interference-free or filled by an additional task. Their results showed reduced memory recognition for both groups of patients in the presence of interference, which was related to impairments in disengaging and engaging attention between the interference and probe stimuli. Together, these data confirm our findings and lead us to emphasize that susceptibility to high demand interference appears to be one of the mechanisms that underlie memory failures in MCI.

According to recent findings, handling interruption during WM maintenance requires task-switching abilities (Clapp and Gazzaley, 2012), in which the delayed response to the encoded information competes with the processing of the interruption stimulus. More specifically, this kind of challenge requires complex executive processing: the sum of the individual sub-components (WM, task-switching) and sub-objectives (maintenance of memory while performing a secondary task and then going back to the memoranda) must be maintained, allowing for the main goal of the task to be achieved (recognition of the encoded information). Considering these processes as

a unit, they could be addressed by the *Branching* model proposed by Koechlin, Basso, Pietrini, Panzer & Grafman (1999). This model postulates a sequential cascade of processes (sub-objectives) necessary to acquire a main objective. Under this framework, we can assert that a failure in any of the processes and/or in their simultaneous management during memory retention could be a responsible factor in forgetting.

It is interesting to note that the presence of interruption revealed a higher depletion of memory than the presence of distraction in all of the participants and under both memory loads. This fact is supported by larger RTs in the more demanding condition, which reveals the necessity of additional cognitive resources. However, the MCI participants systematically remembered less amount of information than the controls (which is supported by the higher effect of interruption in MCI patients than in controls). These findings confirm the highly demanding nature of interruption, in comparison with distraction, and suggest that MCIs are more vulnerable to higher demanding executive tasks than healthy controls. When these executive functions are demanded during memory processing, it is straightforward to appreciate the higher rates of forgetting in the MCI clinical profile.

Additional analysis of the condition x load interaction showed that memory performance was reduced (worse accuracy and longer RTs) in each condition (NI, DIS and INT) when the amount of information to be held in memory increased from one to two items. In agreement with previous literature showing depletion of cognitive resources by means of WM loading (Miller, 1956; Cowan, 2001; Cappell et al., 2010; Kessels et al., 2010), our data confirm that higher cognitive demands (e.g., memory loading and introduction of interference) lead to a greater reduction in the capacity to adequately encode, maintain and retrieve information from memory.

In summary, the current data indicate that handling interference during WM maintenance is a fundamental aspect of memory failures in MCI patients, with a heavy impact on memory in the presence of highly demanding interference. Furthermore, we conclude that interference-based forgetting in MCI potentially stems from deficits in executive processing. Taking into account the potential effect that susceptibility to

interference has on memory and daily living activities, further studies are necessary to advance our understanding of the underlying processes.

One of the limitations of this study is that we did not consider how variables such as cognitive reserve (including occupational attainment, physical, cognitive or leisure activities) or genetic profiles could influence results. However, this study was designed to focus on describing the cognitive mechanisms that underlie memory forgetting in a representative MCI population. The consideration of these abovementioned variables would be interesting for future studies.

# CHAPTER 3. Experiment II

## Distributed theta and alpha oscillatory power increase during memory maintenance in mild cognitive impairment

# 1. AIMS AND HYPOTHESIS

The main objectives of the second study were to study the oscillatory mechanisms underlying successful memory maintenance, and possibly their alterations, in MCI patients, and the relation between the brain oscillatory patterns during memory retention with memory performance and the volume of the hippocampus.

In this experiment, we expected brain oscillatory power deviations from normal patterns, in MCI patients. Any increased oscillatory activity in MCI patients was expected to be related with improved task accuracy, whereas reduced activity will reflect the contrary. Higher accuracy was expected to be related with higher hippocampal volumes.

# 2. METHODS

## 2.1. Participants

A total of 73 volunteers were included in the study. All participants were above 64 years old, right handed handed (Oldfield, 1971), and native Spanish speakers. They were divided into two groups based on their clinical profiles: 39 MCI patients and 34 healthy control adults. Groups were matched in age and educational level (See Table1). Although groups differed in gender distribution, the neurophysiological patterns did not show statistical differences according to gender. MCI patients were recruited from the Geriatrics and Neurology Units of the “Hospital Universitario San Carlos” and the “Memory Decline Prevention Center”, both in Madrid, Spain. Healthy volunteers were recruited from the “Seniors Center of Chamartin District”, Madrid.

All participants were screened by replicating the standardized neuropsychological diagnostic instruments from Experiment I.

Participants were free of significant medical, neurologic and/or psychiatric diseases (other than MCI), including the absence of significant cerebral-vascular disease (i.e. modified Hachinski score ≤ 4) or depressive symptomatology (i.e. Yesavage's Depression Scale scores > 9), and were not using drugs which could affect MEG activity (including cholinesterase inhibitors). According to their clinical and neuropsychological profile, patients were diagnosed as *amnesic-multidomain MCI* (Petersen, 2004).

Prior to the MEG recording, all subjects signed an informed consent that explained the technical and ethical considerations of the investigation. The study was approved by the local Ethics Comitee.

| | Controls | MCI | Stats |
|---|---|---|---|
| **Age** | 71.78 ±4.93 | 73.08±4.42 | $X^2(1)=1.33$, p>0.05 |
| **Education** | 3.21±1.11 | 2.77±1.19 | $X^2(1)=2.95$, p>0.05 |
| **Gender (F/M)** | 28/6 | 21/18 | $X^2(1)=6.59$, p=0.01* |
| **MMSE** | 29.26±0.86 | 27.67±1.91 | $X^2(1)=12.94$, p<0.001* |

Table 1: Mean, standard deviation and statistics comparing groups for age, education, gender (F, female; M, male), and MMSE (minimental state examination test) scores of controls and subjects with MCI.

## 2.2. Experimental paradigm

The stimuli utilized for the experimental paradigm consisted of neutral anonymous male and female faces across a large age range. Hair and ears were removed digitally to avoid non face specific cues. The experiment was computerized through E-prime1.2 software (Psychology Software Tools, Inc.).

Participants performed a delayed recognition WM task (replicating the No Interference, NI, condition from Experiment I) consisted of three main phases: encoding, maintenance and recognition. The only difference from the design of the NI condition from Experiment relied on the number of trials. The present Experiment consisted of four blocks containing randomly presented 32 trials each, with a total of

128 trials per participant. To ensure an adequate attention level across the task, short breaks were offered to participants between blocks in which they were instructed to relax without making movements.

Before the task, instructions were given to participants and all of them underwent a practice session which ensured an adequate understanding. See Figure1 for representation of the experimental paradigm.

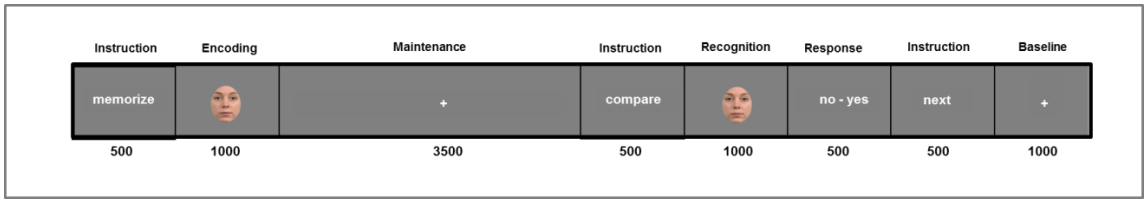



Figure 1. Representation of the experimental paradigm. The experimental paradigm consisted of a delayed recognition WM task under one load. The experimental task was structured in three main phases: encoding, maintenance and recognition.

## 2.3. Data acquisition

MEG signal was acquired with a 306-channel Vectorview system (Elekta-Neuromag) which combines two orthogonal planar gradiometers and one magnetometer. The MEG system was placed in a magnetically shielded room (Vacuum Schmelze GmbH, Hanua, Germany) at the *Centre of Cognitive and Computational Neuroscience* (UPM-UCM, Madrid, Spain). Participants we were asked to avoid making movements. The MEG signal was acquired at a sampling frequency of 1000 Hz (online bandpass filtering at 0.1-330Hz). The head movement was controlled by means of head-position information (HPI) with coils attached to the scalp. HPI coils' position and participants' headshape were defined using a 3D digitizer (FastrakPolhemus) referenced to three anatomical (fiducial) locations: the nasion and the left and right preauricular points. Blinks were monitored by two bipolar electrodes attached above and below the left eye and one electro attached to the lower cheek/ear (ground).

MRI images were collected using a General Electric 1.5T magnetic resonance (MR) scanner, using a high-resolution antenna and a homogenization PURE filter. 3D T1

weighted anatomical brain MRI scans were acquired with a Fast Spoiled Gradient Echo (FSPGR) sequence with parameters: TR/TE/TI = 11.2/4.2/450 ms; flip angle 12º; 1 mm slice thickness, a 256x256 matrix and FOV 25 cm.

## 2.4. Data analysis

### MEG data analysis

Recordings were offline filtered and corrected for head movements with a TSSS-MC spatial filter (Taulu and Kajola, 2005) with a correlation threshold of 0.9, and 10 seconds time window using ELEKTA software. Posterior preprocessing of MEG data was performed using the open source Matlab toolbox Fieldtrip (version 2013-01-02; http://www.ru.nl/fcdonders/ fieldtrip/). The preprocessing included band pass filtering in the range [0.5 150] Hz, notch filter at 50 Hz and harmonics, detrend and baseline correction considering a rime window lasting for 500 ms. Magnetometers were considered for analysis. The current analysis was based on correct responses. Epochs were defined from the continuously recorded MEG signals from -2000 to 5000 ms with respect to the onset of the visual stimulus. Eye blinks, muscle activity, or jump artifacts contaminating the signal were automatically detected using Fieldtrip routines.

The analysis of the signals included Independent component analysis (ICA), with a posterior wavelet filter, and time-frequency analysis of the components.

ICA of the MEG signals with a posterior wavelet filter (wICA, Castellanos and Makarov, 2006) was performed under 2 goals: 1) ensure the artifact correction by subtracting those components responsible for the artifact but recovering the neuronal contribution, and, 2) identify the components of the maintained activity. The so called infomax algorithm proposed by Bell and Sejnowski (1995), and further modified byAmari et al. (1996) and Lee et al. (1999), was applied. It is implemented in EEGLAB MatLab toolbox (Delorme and Makeig, 2004) and available at http://sccn.ucsd.edu/eeglab.

ICA is based on the assumption that the MEG signals are a spatially stable linear mixture of a priori unknown temporarily independent components, including artifactuals and original neuronal activity. Thus, has been proven useful for suppression of artifacts in EEG and MEG recordings arising from several parts of the brain, scalp, and body. ICA involves the separation of measured signals into statistically independent components, allowing the identification of those components that account for artifacts (artifactual componnets). These artifactual components are thereafter cancelled and the free of artifact signals are reconstructed by the linear combination of the remaining components.

However, the components capturing artificial contributions into the signal frequently contain neuronal activity. Rejection of such components includes the cancellation of part of this neuronal activity and in consequence, distortion of the artifact free signals (Friston, 1998). In order to recover such relevant signals, an additional step has been proposed to be included in artifact removal procedure: the inclusion of a wavelet filtering of the components that capture the artifact, which allows the cancelation of the corresponding artifactual contribution without affecting the neuronal activity of interest (Castellanos and Makarov, 2006). This method, named wavelet independent component analysis (wICA), ensures artifact removal without alteration of the spectral and connectivity properties of the neuronal signal. Therefore, wICA was estimated for the pre-established epoch (form -2000 to 5000 ms from the stimulus onset) from a set of 102 time series simultaneously recorded. This process allowed removing those components responsible for artifacts and extracting the artifact-free components of the brain signals.

After wICA, Time–Frequency (TFR) representations of all the components were estimated to each time-window of interest. The time-windows of interest included the baseline period (from -1100 to -1600 ms before the onset of the encoding stimulus) and the memory maintenance period (from 1500 to 5000 ms after the onset of the encoding stimulus). Morlet wavelets were used with a width of five cycles per wavelet in the frequency range [1, 150] Hz with 1Hz steps. The resulting TFR representations of the maintenance period indicated the contribution of every component to the sustained activity along this period. This was evident when a randomly recursive

removal of one component was sufficient to break down the spectral stability observed when including all the components into the TFR representation. Therefore, all components were also considered for TFR representation of the baseline period. The frequency range of the TFR representations was averaged in standard spectral bands: delta ([1 4] Hz), theta ([4 8] Hz), alpha ([8 12] Hz), beta ([12 30] Hz) and gamma ([30 60] Hz). Each spectral band of the memory retention period was baseline corrected.

Aiming to study the localization of the TFR representations of memory retention in the brain, topography maps of each spectral band were studied in each participant. This procedure was performed for a solely time-window (by averaging the TFR representation of the memory delay period; from 1500 ms to 5000 ms respect to the onset of the encoding stimulus) and for several sub-windows to evaluate potential topography changes over time (averaging the TFR representation of 100 ms time-windows; from 1500 to 5000 ms of the memory delay period). The resulting topographies showed distributed maps between spectral bands, time-windows, trials and participants. These results indicated that the spectral representation of the memory-sustained activity in this sample of participants is not localized in a unique brain region, but is distributed across the brain. Therefore, the TFR values of each frequency band were averaged across time for the memory delay period (from 1500 ms to 5000 ms as a unique time-window) and for the baseline period (from -1100 ms to -1600 ms). From now, we will name this measure as join-IC-TFR.

**Statistical analysis**

Non-parametric approaches based on the Kruskal Wallis test were applied to evaluate potential statistical differences of the TFR values within and between groups. The following comparisons were performed: baseline vs. memory maintenance in MCI and in control participants separately; baseline of MCIs vs. baseline of controls; memory retention of MCIs vs. memory retention of controls. To control the family-wise error due to multiple comparisons, the test distribution was derived from a permutation test (Ernst, 2004). This procedure randomly assigns subjects as belonging to one of the groups, keeping the original number of subjects and then performing a non-parametric

test in these two new groups. This procedure was repeated 5000 times to compute a p-value distribution. After identifying the 5th percentile of each distribution, only p-values below that threshold were accepted.

Finally, relations between the spectral values of memory maintenance, cognitive performance and hippocampal volumes were analyzed using Spearman correlation procedure. Analysis will be based on thee frequency ranges showing significant differences between groups.

### MRI data analysis

Freesurfer software package (version 5.1.0; http://ftp.nmr.mgh.harvard.edu/) was used for automatic sub-cortical segmentation the high-resolution T1-weighted images (Fischl, et al., 2002), assigning a label to the sub-cortical brain regions. The labelling procedure is based on probabilistic information automatically estimated from a manually labelled training set. Hippocampal volume was extracted in cubic millimetres (mm3) and normalized by the total grey matter volume (Hipp/GM) for each participant. Non-parametric approaches based on the Kruskal Wallis test were applied to evaluate potential differences in hippocampal volume ratios between groups.

## 3. RESULTS

### 3.1. Performance

Analysis of the delayed recognition WM performance revealed no significant differences between controls and MCI, neither in accuracy nor in reaction times (RT). See Table2 for performance and stats.

| | Controls | MCI | Stats |
|---|---|---|---|
| **Accuracy (%)** | 83.8±7.24 | 82.6±9.03 | $X^2(1)=0.25$, p>0.05 |
| **RT (ms)** | 994.1±294.67 | 1074.9±318.39 | $X^2(1)=1.1$, p>0.05 |

Table 2. Task performance of controls and MCIs. Accuracy shows the percentage (%) of correct responses. Reaction time (RT) shows the time in milliseconds, (ms). Means, standard deviations and statistics between groups are shown.

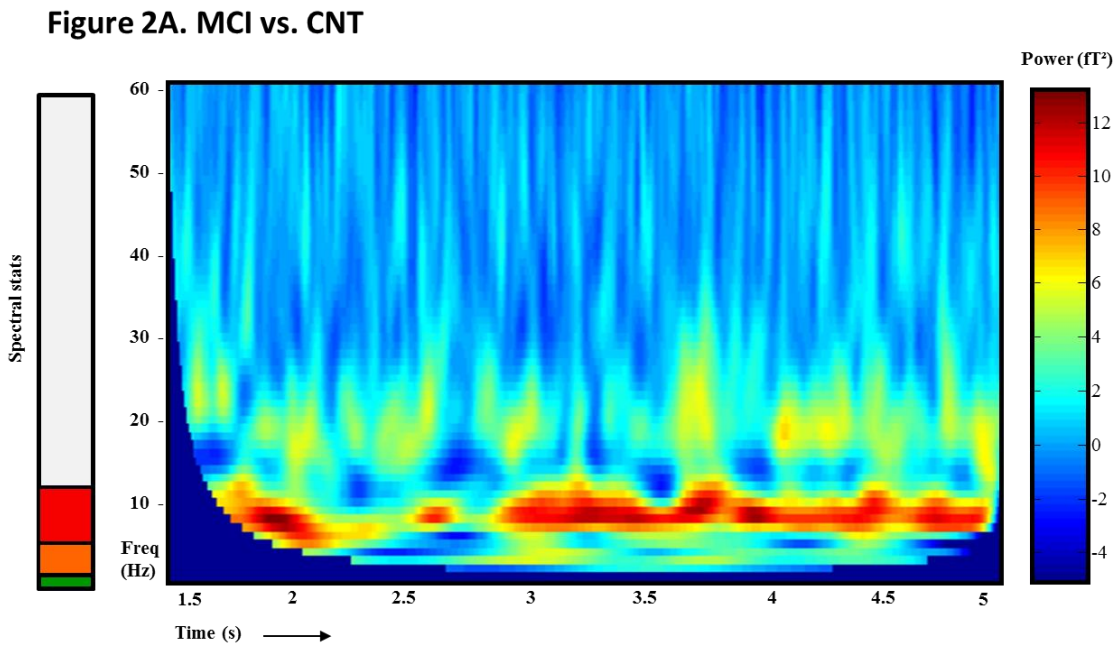
### 3.2. Oscillatory memory maintenance

The statistical analysis of the join-IC-TFR between baseline and memory delay period revealed that memory maintenance elicited a power increase in theta and alpha frequency bands in both groups of participants (MCI: theta: $p<0.005$; alpha: $p<0.005$; controls: theta: $p=0.001$; alpha: $p<0.0005$). No differences were observed I the beta and gamma frequency bands in any of the groups ($p>0.05$).

Comparison of the join-IC-TFR power values of the baseline period between groups revealed no differences in any of the frequency bands (theta: $p>0.05$; alpha, $p>0.05$; beta $p>0.05$; gamma: $p>0.05$).

Comparison of the join-IC-TFR values of the memory maintenance period (baseline corrected) between groups revealed significant increased power values in MCI patients in the theta ($p<0.005$) and alpha ($p<0.0005$) frequency bands comparing with controls. No significant differences were found neither in delta ($p>0.05$) nor in beta ($p>0.05$) and gamma ($p>0.05$) frequency bands between groups. Figure 2A shows the subtraction of the join-IC-TFR values for MCI relative to the controls'. Figure 2B shows the time course of theta and alpha power for the MCI and the control group.

Further analysis revealed significant inverse relation between the power of alpha frequency band and task accuracy in MCI patients ($r = -0.41$, $p = 0.009$). No significant relations were found between alpha power and RT of the experimental paradigm ($p>0.05$) neither between alpha power and neuropsychological scores (all comparisons: $p>0.05$) in MCI patients. Healthy controls showed no significant correlation between alpha power values and task performance and neuropsychological scores (all comparisons: $p>0.05$). Theta power values showed no significant relation neither with task performance neither with neuropsychological scores in any of the two groups of participants (all comparisons: $p>0.05$). See Figure 2C.



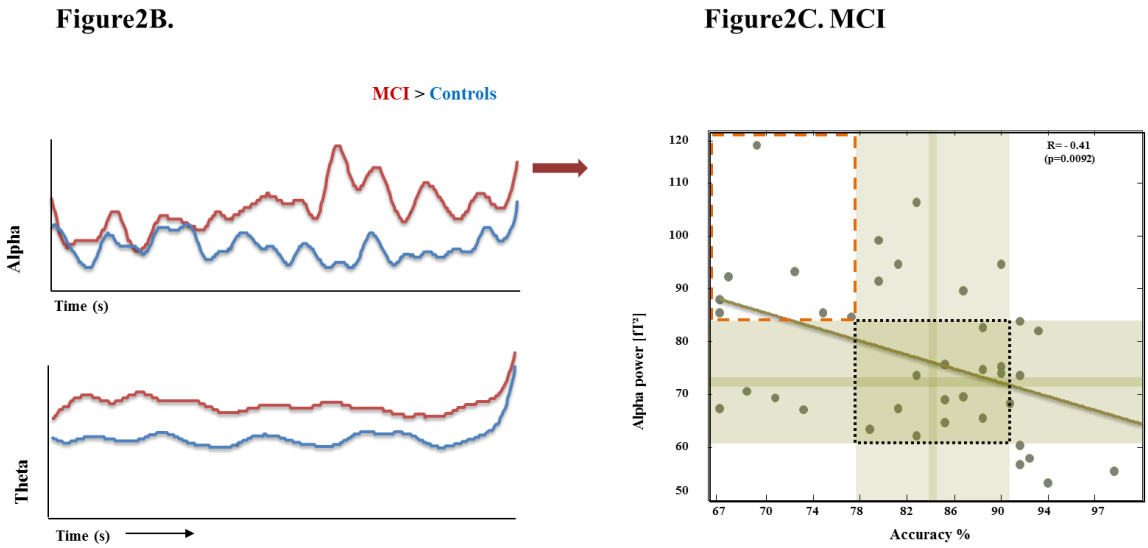




Figure 2. Time-frequency representation. A) Comparison of the oscillatory activity during the memory maintenance period between groups (spectral power of MCIs – spectral power of controls). X axis shows the time-course of the memory maintenance period (1500 5000 ms after the stimulus onset). The Y axis shows the frequency range (1-60 Hz). The colorbar in right shows the power values of each frecuency ($fT^2$). The colorbar in left shows, in a color-code illustration, the statistical robustness of the comparison between MCI and controls. B) Time courses of the power in theta and alpha spectral bands for MCIs (red line) and for controls (blue line) along the memory maintenance period. C) Correlation between task accuracy (%) and time-averaged alpha power of MCI participants. Highlighted areas in green denote the mean and standard deviation of alpha and task accuracy (± 1 std) of controls. The dotted square in orange indicates patients with higher alpha and reduced memory accuracy values.

### 3.3. Correlations with hippocampal volume

Analysis of hippocampal volume ratios, left/right Hipp/GM, (mean and standard deviations; Controls: Left Hipp/GM=6.31(0.76), Right Hipp/GM=6.3(0.52); MCIs: Left Hipp/GM=5.49(0.8), Right Hipp/GM=5.48(0.94)) between groups revealed significant atrophy (in both left and right hippocampus) in MCI patients compared with healthy adult controls (stats between groups; Left Hipp/GM, $X^2(1)=10.84$, p=0.01; Right Hipp/GM, $X^2(1)=10.5$, p=0.01). Figure 3B shows two representatives T1 weighted anatomical brain images emphasizing the decrease of hippocampal volumes in MCI with respect to controls.

Negative relations were found between Hipp/GM and theta and alpha power values in MCI patients. Healthy controls showed significant negative relation between left Hipp/GM and alpha power, whereas no correlation was found for Hipp/GM and theta power values. See Table 3 and Figure 3 right panels.

Additionally, MCI patients revealed a positive relation between Hipp/GM and MMSE and delayed memory recall test (of the WMS-III) scores, and a trend towards significance between Hipp/GM and task accuracy. See Table 4 for correlational results.

| | Controls<br>Alpha power | MCI<br>Theta power | MCI<br>Alpha power |
|---|---|---|---|
| **Left Hipp / GM** | -0.564 (0.018) | -0.618 (0.001) | -0.581 (0.0023) |
| **Right Hipp / GM** | - | -0.461 (0.002) | -0.418 (0.037) |

Table 3. Correlations between hippocampal volume rates and time-averaged power values of theta and alpha frequency bands. Hipp, hippocampus; GM, grey matter. Correlation coefficients and corresponding p-values are shown.

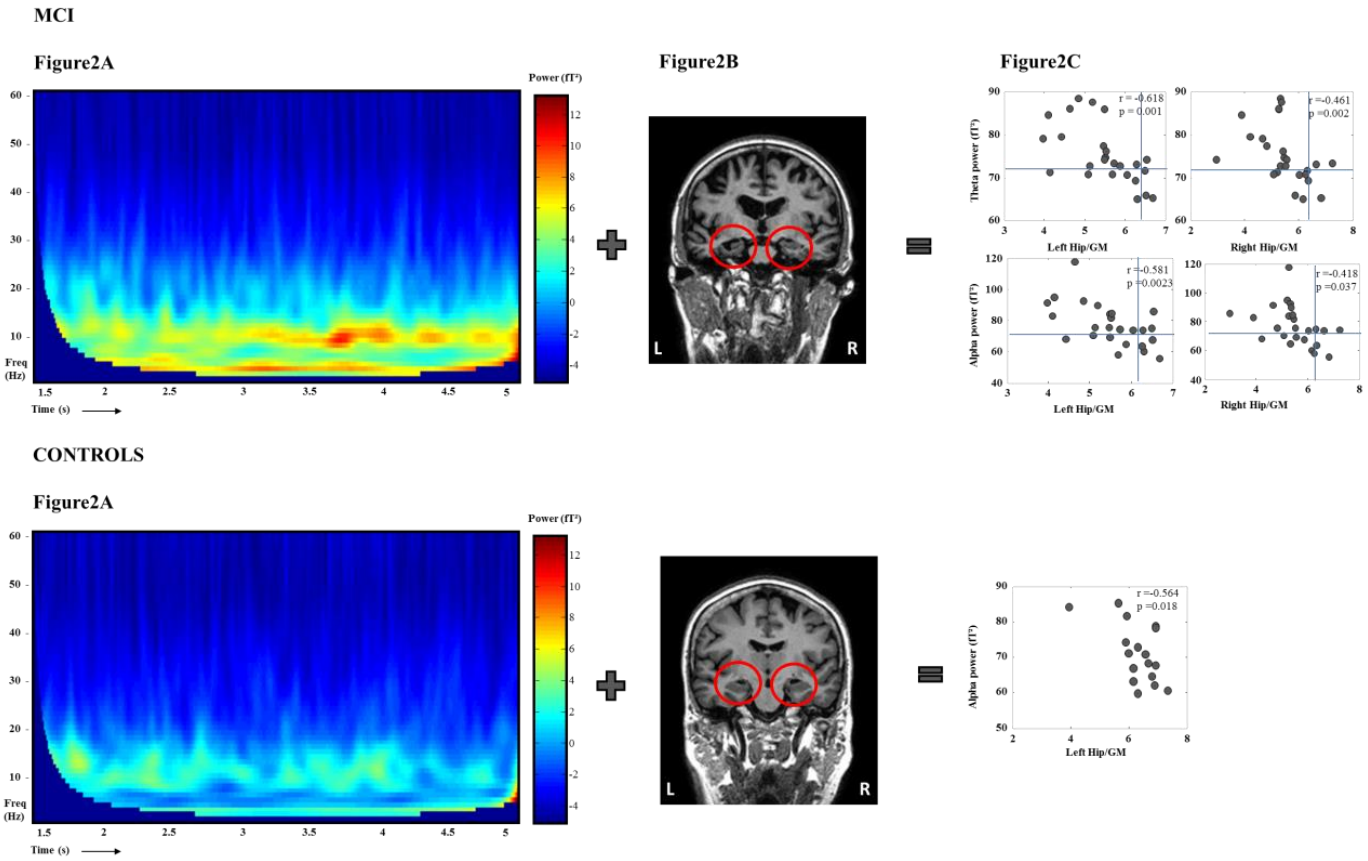



Figure 3. Time-Frequency representations and correlations with hippocampal volumes for each group of participants, MCIs and controls. A) Time-Frequency representation of all the components along the maintenance period for MCI (top panels) and controls (below panels). B) Two illustrative MRI images showing hippocampal volumes of MCI and controls (MCIs show reduced hippocampal volumes). C) Correlations between hippocampal volume ratios (normalized to the total grey matter, GM) and theta and alpha power of the maintenance period. Vertical and horizontal lines in blue in top panels show the mean values of the hippocampal volume ratios and spectral power of controls.

| | Acc | MMSE | Del. Recall |
|---|---|---|---|
| **Left - GM** | | 0.42 (0.039) | 0.58 (0.002) |
| **Right - GM** | 0.38 (0.056) | | 0.38 (0.059) |

Table 4. Correlations between hippocampal volume ratios and cognitive status (Acc, task accuracy; MMSE minimental state examination; Del. Recall, delayed recall subtest of the Wechsler Memory Scale). Correlation coefficients and corresponding p-values are shown.

## 4. DISCUSSION

To the best of our knowledge, this is the first study investigating the dynamic oscillatory patterns underlying visual WM retention in MCI patients. The current findings revealed increased oscillatory power of theta and alpha frequency bands during memory retention in MCI patients, in comparison with healthy controls. Furthermore, patients showed negative relations between the power values of these two frequency bands, hippocampal volume ratios and task performance.

The maintenance of information in WM is an essential and complex process which is revealed by stable oscillatory activity in the brain (Goldman-Rakic, 1995; Wang et al., 2011). Specific rhythms, like theta and alpha frequency ranges, have been proposed to play a leading role in the retention of WM representations (Jensen et al., 2002; Sauseng et al., 2010). Thus, any imbalance in these spectral bands can underlie memory impairments in the normal and pathological aging brain (Schnitzler and Gross, 2005).

The essential presence of sustained activity of theta and alpha oscillatory bands during memory retention periods is nowadays a robust finding in the literature (Gevins et al., 1997; Raghavachari et al., 2001; Jensen and Tesche, 2002; Johnson et al., 2011; Klimesch et al., 2005, 2008; Lee et al., 2005; Sauseng et al., 2010). Our results indicated increased sustained theta and alpha power in both groups of participants during the maintenance period when compared with the baseline. Therefore, in line with the

abovementioned literature, our data confirm the involvement of these two frequency bands in WM retention.

However, MCI participants of the present study showed an overuse of these mechanisms in the theta and alpha frequency bands when compared with controls. Traditionally, increased brain activity during cognitive tasks in aging has been attributed to compensatory mechanisms. This neuronal overactivation has been consciously related with maintenance of certain cognitive status and/or task performance due to the recruitment of contralateral and/or prefrontal regions of the brain (Reuter-Lorenz, 2002; Grady, 2012). This phenomena is in line with a large body of literature evidencing compensatory mechanisms MCI patients by increased brain oscillatory activity (Maestú et al., 2008; Bajo et al. 2010; Aurtenetxe et al. 2013; Missonnier et al. 2006), as well as the blood flow (Dickerson et al, 2005; Bokde et al, 2010; Grady et al., 2003, 2005) during memory tasks. MCI patients of our study matched memory performance to that of controls. Thus, the sustained increased oscillatory activity in the theta and alpha frequencies tempt to be associated with compensatory mechanisms that allow achieving the similar level of performance. However, the role of the increase in oscillatory activity in MCI remains unclear and interpretations should be taken with caution.

Nowadays, a possible causal relation between increased brain activity and altered pathophysiology is being investigated (Sperling et al., 2010). Accumulation of amyloid-ß in the brain is considered one of the central causes in the pathogenesis of Alzheimer's disease, AD (Selkoe, 2001). Furthermore, it is associated with a widespread brain network dysfunction in preclinical and prodromal stages of AD (Sperling et al., 2010; Drzezga et a., 2011). Studies from animal models of AD show that intermediate levels of amyloid-ß accumulation lead to synaptic excitation in neurons placed in the vicinity (Busche et al., 2008), whereas high levels of accumulation lead to synaptic depression (Palop and Mucke, 2010). Furthermore, amyloid-ß plaques are implicated in the dysfunction and reduction of the number of GABAergic inputs to pyramidal cells (Krantik et al., 2012; Garcia-Marin et al., 2009), which lead to a decreased inhibitory control and to a higher excitation of the cell. In this line, GABA concentrations have

been observed to modulate brain oscillations in animals (Smythe et al., 1992; Golebiewski et al., 1996) and recently in humans (Yoon et al., 2010; Rowland et al., 2013). Interestingly, in vivo imaging research has recently shown brain hyperactivity patterns in amyloid-positive individuals during memory-association tasks (Spearling et al., 2009; Vannini et al., 2011). Taking all this together on the well-known accumulation of amyloid-ß plaques in MCI pathology (Ref), the increased oscillatory power observed in patients could indirectly reveal the neuropathological processes accounting in the MCI brain.

To test the compensatory or pathological character of the increased oscillatory activity in patients, a series of correlation analysis leaded us to interpret alpha as reflecting pathology and theta as reflecting compensation. Correlation analysis revealed that patients with higher alpha power were those with reduced WM accuracy, whereas this correlation was not found in healthy controls. Furthermore, those participants who showed greater alpha power showed reduced hippocampal volume ratios. These inverse relations drop down any compensatory interpretation and open a new perspective for the role of alpha band in the MCI pathology. Support for these results come from research showing negative relationship between hippocampal activation and memory performance in MCI patients (Putcha et al., 2011). Taking these data together, the present study indicates that the progression of pathology in the brain from normal to pathological aging may lead to a progressive increase of the alpha oscillatory activity during WM retention. Furthermore, when activity in this frequency range reaches certain levels as accounts in MCI, drops down memory retention abilities. More advanced research, which evaluates alpha modulations under several task difficulties and cognitive states, would be needed to further evaluate such a hypothesis.

A remaining question now is how, in the presence of aberrant brain oscillatory activity, MCI patients were able to match controls' performance. The lack of correlation between theta power and WM performance does not allow to fully interpreting the role of this frequency band. However, power of beta and gamma frequencies was similar between groups and oscillatory power of theta was negatively

related with hippocampal volume rates in patients but not in healthy controls. Therefore, these data lead to indicate a potential implication of increased theta in successful WM retention in MCI patients, indicating its potential compensatory nature. A duality process in the MCI oscillatory spectra has been described previously (Aurtenetxe et al, 2013; Refs fMRI) indicating that pathological and compensatory mechanisms coexist at this stage of the disease. Support for this interpretation arises from an EEG study which showed reduced theta power in the presence of reduced performance during memory recognition (Cummins et al., 2008). Further studies evaluating theta activity modulations across several memory loads would offer important evidence about the role of this frequency range in memory retention of MCI population.

An additional remarkably finding of the current study refers to the widespread distribution of the oscillatory activity in the brain, with no privileged localization across trials and participants. In addition, the persistence presence of the oscillatory activity during WM retention resulted from the contribution of all the components extracted from the ICA analysis. These data support the notion of memory retention as a distributed phenomenon between several temporally-coordinated regions in the brain (Sarnthein et al., 1998; Lisman and Idiart, 1995; Miller and Desimone, 1994; Palva et al., 2010, 2011; Raghavachari et al., 2001), and could be integrated in the framework of Fuster and Bressler (2012) which postulates that “memory, comprises a large array of distributed, overlapping, and interactive networks”.

# CHAPTER 4. Experiment III

## Reduced theta power after interruption is responsible for working memory forgetting in mild cognitive impairment

# 1. AIMS AND HYPOTHESIS

The main objectives of the third experiment were to study the effect of interference on the oscillatory mechanisms underlying successful and non-successful memory maintenance in MCI patients, and the relation between the brain oscillatory patterns with performance and volume of hippocampus.

In this experiment, we expected reduced accuracy for the interruption condition in MCI patients, comparing with controls. Successful WM was expected to be related with increased oscillatory activity probably in both, pre and post interruption periods of the task, and with higher hippocampal volumes in MCI patients. Contrary, WM forgetting was expected to be related with reduced oscillatory activity, possibly in the period after interruption, and with reduced hippocampal volumes.

# 2. METHODS

## 2.1. Participants

A total of 44 volunteers were included in the study. All participants were above 65 years old, right handed handed (Oldfield, 1971), and native Spanish speakers. They were divided into two groups based on their clinical profiles: 22 MCI patients and 22 healthy control adults. Groups were matched in age, gender and educational level (see Table1). MCI patients were recruited from the Geriatrics and Neurology Units of the "Hospital Universitario San Carlos" and the "Memory Decline Prevention Center", both in Madrid, Spain. Healthy volunteers were recruited from the "Seniors Center of Chamartin District", Madrid.

All participants were screened by replicating the standardized neuropsychological diagnostic instruments from Experiments I and II.

Participants were free of significant medical, neurologic and/or psychiatric diseases (other than MCI), including the absence of significant cerebral-vascular disease (i.e. modified Hachinski score ≤ 4) or depressive symptomatology (i.e. Yesavage's Depression Scale scores > 9), and were not using drugs which could affect MEG activity

(including cholinesterase inhibitors). According to their clinical and neuropsychological profile, patients were diagnosed as *amnesic-multidomain MCI* (Petersen, 2004).

Prior to the MEG recording, all subjects signed an informed consent that explained the technical and ethical considerations of the investigation. The study was approved by the local Ethics Comitee.

| | Controls | MCI | Stats |
|---|---|---|---|
| **Age** | 71.78 ±4.93 | 73.08±4.42 | $X^2(1)=1.47$, $p>0.05$ |
| **Gender (F/M)** | 16/6 | 14/8 | $X^2(1)=4.86$, $p>0.05$ |
| **Education** | 3.21±1.11 | 2.77±1.19 | $X^2(1)=2.38$, $p>0.05$ |
| **MMSE** | 29.26±0.86 | 27.67±1.91 | $X^2(1)=11.02$, $p<0.01$ * |

Table 1: Mean, standard deviation and statistics comparing groups for age, gender (F, female; M, male), education and MMSE (minimental state examination test) scores of controls and subjects with MCI. Asterisk (*) shows statistical significance between groups below 0.05.

## 2.2. Experimental paradigm

The stimuli utilized for the experimental paradigm consisted of neutral anonymous male and female faces across a large age range. Hair and ears were removed digitally to avoid non face specific cues. The experiment was computerized through E-prime1.2 software (Psychology Software Tools, Inc.).

Participants performed a delayed recognition WM paradigm consisted of two conditions: no interference (NI) and interruption (INT), see Figure 1 for a representation of the experimental paradigm. Instructions for execution of NI and INT are described in the behavioural study of the present Thesis (Chapter I). The main difference between both studies relays on the number of trials. For the present MEG study, as for the Experiment II of thee Thesis, NI and INT conditions consisted of four blocks containing randomly presented 32 trials each. Each participant performed a total of 128 trials of each condition. The 16% of the trials regarding the INT condition were trials to which participants were instructed to make the button press to the

interruption stimulus. Therefore, to avoid any potential artefact, these trials were discarded from the MEG data analysis. The same number of trials was randomly discarded from the NI condition for the Meg analysis. To ensure an adequate attention level across the task, short breaks were offered to participants between blocks, in which they were instructed to relax without making movements. Before the task, instructions were given to participants and all of them underwent a practice session which ensured an adequate understanding. Conditions were counterbalanced across participants.

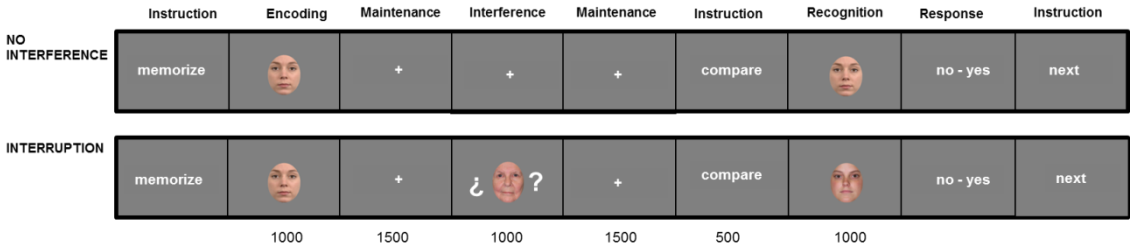



Figure 1. Representation of the experimental paradigm. The experimental paradigm consisted of two conditions: No interference and Interruption. Both conditions were structured in three main phases: encoding, maintenance and recognition, and involved one memory load.

## 2.3. Data acquisition

MEG signal was acquired with a 306-channel Vectorview system (Elekta-Neuromag) which combines two orthogonal planar gradiometers and one magnetometer. The MEG system was placed in a magnetically shielded room (Vacuum Schmelze GmbH, Hanua, Germany) at the *Centre of Cognitive and Computational Neuroscience* (UPM-UCM, Madrid, Spain). Participants we were asked to avoid making movements. The MEG signal was acquired at a sampling frequency of 1000 Hz (online bandpass filtering at 0.1-330Hz). The head movement was controlled by means of head-position information (HPI) with coils attached to the scalp. HPI coils' position and participants' headshape were defined using a 3D digitizer (FastrakPolhemus) referenced to three anatomical (fiducial) locations: the nasion and the left and right preauricular points. Blinks were monitored by two bipolar electrodes attached above and below the left eye and one electro attached to the lower cheek/ear (ground).

MRI images were collected using a General Electric 1.5T magnetic resonance (MR) scanner, using a high-resolution antenna and a homogenization PURE filter. 3D T1 weighted anatomical brain MRI scans were acquired with a Fast Spoiled Gradient Echo (FSPGR) sequence with parameters: TR/TE/TI = 11.2/4.2/450 ms; flip angle 12º; 1 mm slice thickness, a 256x256 matrix and FOV 25 cm.

## 2.4. Data analysis

### MEG data analysis

Data preprocessing was equal for NI and for INT conditions. Recordings were offline filtered and corrected for head movements with a TSSS-MC spatial filter (Taulu and Kajola, 2005) with a correlation threshold of 0.9, and 10 seconds time window using ELEKTA software. Posterior preprocessing of MEG data was performed using the open source Matlab toolbox Fieldtrip (version 2013-01-02; http://www.ru.nl/fcdonders/fieldtrip/). The preprocessing included band pass filtering in the range [0.5 150] Hz, notch filter at 50 Hz and harmonics, detrend and baseline correction considering a time window lasting for 500 ms. Magnetometers were considered for analysis.

The current analysis was based on correct and incorrect responses separately. Epochs were defined from the continuously recorded MEG signals from -2000 to 5000 ms with respect to the onset of the visual stimulus. Eye blinks, muscle activity, or jump artifacts contaminating the signal were automatically detected using Fieldtrip routines. To avoid potential artifacts from motor responses to the 2in relation to the

The analysis of the signals from each condition and response type (correct and incorrect responses) separately, included independent component analysis (ICA) with a posterior wavelet filter. This analysis was performed as described in Experiment II. The posterior time-frequency analysis of the components was performed as well as in Experiment II, with differences relaying in the time-windows utilized. In the present third Experiment, the time-windows of interest were the following: the called pre-interference period (including a time-window of 1000 ms, from 1500 to 2500 ms after

the onset of the encoding stimulus) and the called post-interference period (including a time-window of 1000 ms, from 4000 to 5000 ms after the onset of the encoding stimulus). These time-windows were utilized for both the NI and the INT conditions.

After wICA, Time-Frequency (TFR) representations of all the components were estimated to each time-window of interest, pre-interference and post-interference periods. Morlet wavelets were used with a width of five cycles per wavelet in the frequency range [1, 150] Hz with 1Hz steps. The frequency range of the TFR representations was averaged in standard spectral bands: delta ([1 4] Hz), theta ([4 8] Hz), alpha ([8 12] Hz), beta ([12 30] Hz) and gamma ([30 60] Hz). The TFR values of, each spectral band, regarding each condition, each response type (hits and errors) and time-window of interest (pre-interference and post-interference) were baseline corrected and afterwards averaged across time.

The analysis of the current Experiment was focused on the INT condition. For that purpose, TFR values of each time-window of interest and response type of the INT condition (previously baseline corrected) were normalized by its respective TFR values from the NI condition. Therefore, statistical analysis and results will show results regarding the INT condition, normalized by the NI condition.

**Statistical analysis**

Non-parametric approaches based on the Kruskal Wallis test were applied to evaluate potential statistical differences of the TFR values within and between groups. The following comparisons were performed: pre-interference vs. post-interference WM retention in MCI and in control participants separately, and for each response type separately (hits and errors); pre-interference period of MCIs vs. pre-interference period of controls; post-interference period of MCIs vs. post -interference period of controls. To control the family-wise error due to multiple comparisons, the test distribution was derived from a permutation test (Ernst, 2004). This procedure was repeated 5000 times to compute a p-value distribution. After identifying the 5th percentile of each distribution, only p-values below that threshold were accepted.

Finally, relations between the spectral values of each WM retention period and response type, cognitive performance and hippocampal volumes were analyzed using Spearman correlation procedure. Analysis will be performed on the frequency ranges showing significant differences between groups.

**MRI data analysis**

Freesurfer software package (version 5.1.0; http://ftp.nmr.mgh.harvard.edu/) was used for automatic sub-cortical segmentation the high-resolution T1-weighted images (Fischl, et al., 2002), assigning a label to the sub-cortical brain regions. The labelling procedure is based on probabilistic information automatically estimated from a manually labelled training set. Hippocampal volume was extracted in cubic millimetres (mm3) and normalized by the total grey matter volume (Hipp/GM) for each participant. Non-parametric approaches based on the Kruskal Wallis test were applied to evaluate potential differences in hippocampal volume ratios between groups.

# 3. RESULTS

## 3.1. Performance

Data from the no interference condition revealed no significant differences between controls and MCI participants, whereas the interruption condition showed a depletion of performance in MCI patients comparing with controls. All participants showed 80% of correct responses to the interruption stimuli which age exceeded 60 years old, indicating an adequate processing of the interruption stimuli, and the response rate was not significant between groups. See Table2 for performance and stats.

| | Controls | MCI | Stats |
|---|---|---|---|
| **NI Hits (%)** | 84.91±7.25 | 79.02±11.27 | $X^2(1)=2.81$, $p>0.05$ |
| **INT Hits (%)** | 69.46±7.02 | 63.17±8.92 | $X^2(1)=5.1$, $p<0.05$ * |

Table 2. Task accuracy of the control and the MCI group. Means, standard deviations and statistics between groups are shown. Asterisk (*) shows statistical significance between groups below 0.05.

### 3.2. Oscillatory activity of the pre and post interruption periods within groups

**Hits**

Statistical analysis of the join-IC-TFR between the pre and post interference periods of hits revealed that MCI patients increased power values of the theta and alpha frequency ranges after the presence of interruption ($p<0.05$). No differences were found in the beta and gamma frequency ranges ($p>0.05$). Analysis of the control group revealed no significant differences between both periods in any of the frequency bands analyzed (all comparisons, $p>0.05$). See Figure 2.

**Errors**

The statistical analysis of the join-IC-TFR between the pre and post interference maintenance periods of errors in the MCI group revealed decreased power values of the theta frequency range in the post interference period ($p<0.05$), whereas alpha power values were increased ($p<0.05$). Analysis of the control group data revealed a trend towards significance in the post interruption period, relative to the pre interruption period, in the alpha frequency range ($p=0.057$), whereas no significant differences were found in the rest of the frequency bands analyzed (all comparisons, $p>0.05$). See Figure 2.

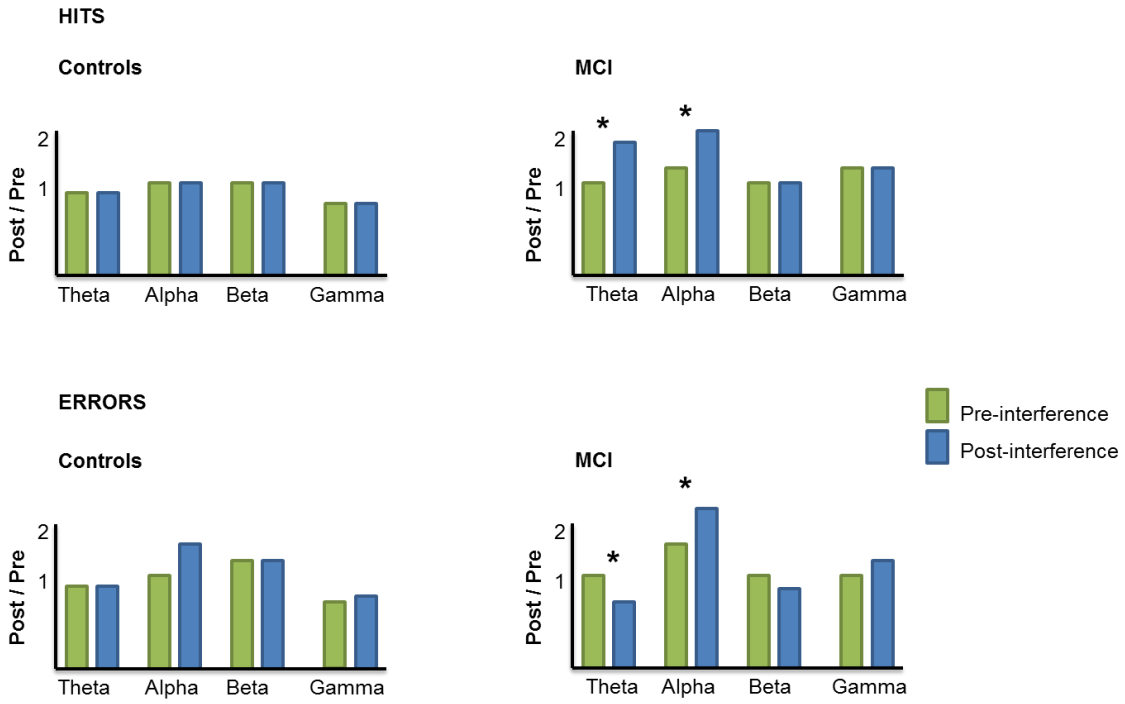



Figure 2. Differences in oscillatory power between pre (in green color) and post (in blue color) interference periods of memory retention in each group of participants. Asterisks (*) show significance below 0.05 between pre and post interference in each group.

### 3.3. Oscillatory activity of the pre and post interruption periods between groups

**Hits**

The statistical analysis of the join-IC-TFR between groups revealed increased theta and alpha power values in the post interruption in the MCI groups, comparing with controls (all $p<0.05$). No differences were found in the beta and gamma frequencies in the post-interference period between groups ($p>0.05$). No differences were found between groups regarding the pre-interference period in any of the frequency bands (all $p>0.05$). See Figure 3.

**Errors**

The statistical analysis of the join-IC-TFR between groups revealed that in the post-interference period of the WM task, MCI patients decreased theta power values ($p<0.05$) and increased power values in the alpha frequency range ($p<0.05$). No

differences were found in the beta and gamma frequencies in the post-interference period between groups (p>0.05). No differences were found between groups regarding the pre-interference period in any of the frequency bands (all p>0.05). See Figure 3.See Figure 3.

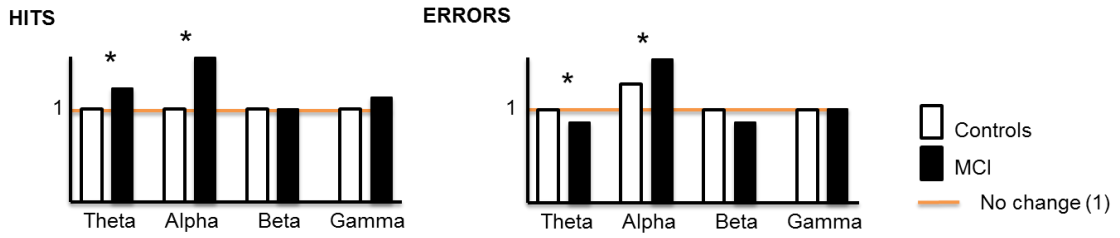



Figure 3. Differences of change in oscillatory power between pre (in green color) and post (in blue color) interference periods of memory retention between groups. Asterisks (*) show significance below 0.05 between groups.

### 3.4. Correlations between power change and task performance

Analysis of the relation between the power change (regarding pre and post interference periods) and task performance, revealed that those MCI patients with higher alpha values in the post-interference period of correct responses (hits) were those with reduced task accuracy (p<0.05).

Additionally, those MCI patients with reduced power in the theta band in the post-interference period of error responses were those with reduced task accuracy (p<0.05). No significant relation between power and task accuracy was found in the control group neither in theta nor in alpha bands (all, p>0.05).

### 3.5. Correlations with hippocampal volume

Analysis of hippocampal volume ratios, left/right Hipp/GM, (mean and standard deviations; Controls: Left Hipp/GM=6.28±0.5, Right Hipp/GM=6.09±0.55; MCIs: Left Hipp/GM=5.36±1.12, Right Hipp/GM=5.55±0.67) between groups revealed significant

atrophy in MCI patients compared with healthy adult controls in the Left Hipp/GM ($X^2(1)=4.86$, $p<0.05$), and a trend towards significance in the Right Hipp/GM ($X^2(1)=3.78$, $p=0.52$). See Figure 4 for a representation of hippocampal volume rates of each group.

Correlation analysis between Hipp/GM and theta and alpha power values in the MCI group revealed negative correlations for accurate responses ($p<0.05$). Analysis of error responses revealed positive relation between Hipp/GM and theta power, and negative relation between Hipp/GM and alpha power ($p<0.05$). Analysis for the control group revealed no significant relation between power values in the theta and alpha frequency ranges and Hipp/GM (all, $p>0.05$).

Additionally, MCI patients revealed a positive relation between Left Hipp/GM and MMSE and between Right Hipp/GM and delayed memory recall test (of the WMS-III) ($p<0.05$).

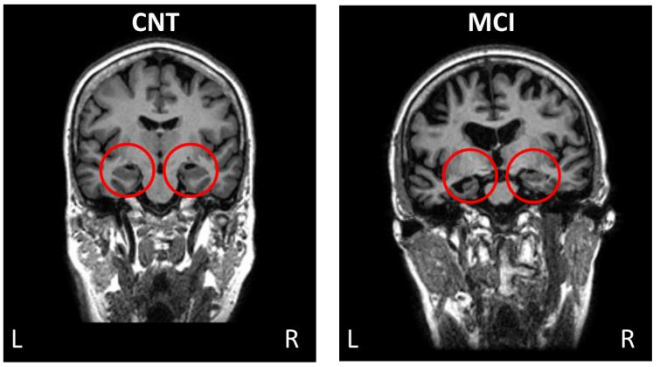



Figure 4. Representation of hippocampal volumes of participants, where Mild cognitive impairment (MCI), in right, shows atrophy in comparison with controls (CNT), in left.

# 4. DISCUSSION

This is the first study investigating the dynamic oscillatory patterns underlying successful retention and forgetting of visual delayed WM information in the presence of interference in MCI patients. The behavioral data of the current study revealed that WM accuracy was more disrupted by interruption in MCI patients that in control participants, replicating the previous findings (Experiment I). The analysis of the neural basis characterizing correct and incorrect WM retention showed that the post-interference period is the one that differentiates patients and controls, both for hits and for error responses. In this sense, during successful WM retention, MCI patients showed increased the power of theta and alpha frequencies, whereas for unsuccessful WM retention, they showed decreased theta and increased alpha power after resolving interference, relative to controls. Interestingly, those patients with higher alpha values were those with reduced number of hits, whereas those with reduced theta values were the ones with higher number of errors. Furthermore, patients with reduced hippocampal volume rates showed higher theta and alpha power for hits, whereas for errors, patients with reduced hippocampal volume rates showed reduced theta and increased alpha power. Altogether, these results offer a new perspective about the role of theta frequency band in retention and forgetting of information in the MCI population.

**The role of theta power in WM retention with interruption in MCI**

The first important results from the current study revealed that relative to controls, MCI participants increased theta power values in the post interference period for successful accuracy.

In line with the current findings, MEG results have shown increased theta activity in MCI patients during memory processes and this increase has been related with higher memory abilities (Aurtenetxe et al., 2012). In addition, higher theta power values in patients of our study, but not controls, were related with reduced hippocampal volume suggesting its relation with pathological processes, and the necessity to recruit

activity in this frequency band to successfully perform the task. Neuroimaging literature shows that the over-recruitment of neurons in the brain allows counterbalancing cognitive alterations in MCI patients and furthermore, acquiring certain level of performance (Dickerson et al., 2005; Grady et al., 2003, 2005; Buckner, 2004). Together, these findings seem to indicate that after handling interruption, the successful reestablishment of the memoranda is modulated by the increase in theta power in MCI patients.

Nevertheless, activity in this frequency band did not correlate with task accuracy for hit responses. Thus, to further elucidate this hypothesis, examination of the oscillatory activity of unsuccessful retention (error trials) is straightforward.

As observed in the brain activity of errors, the power of theta frequency band dropped after the presence of interference in the MCI group. Furthermore, this decrease of activity was related with higher number of errors and greater atrophy of the hippocampus in the same group. In consequence interestingly, these data indicate that after handling interruption, forgetting occurs by a depletion of the activity in the theta frequency band in MCI patients.

Theta frequency range is directly involved in memory processes. Specifically, oscillations in this frequency range have been observed to represent maintenance, monitoring and integration of the information held in memory (Klimesch, 2005, 2008; Sauseng et al., 2010 for a review). In this line, activity in the theta frequency band has been proposed as a mechanism of cognitive control, allowing the monitoring processes such as accounts during interference situations (Nigbur et al., 2011; 2012). Taking together, the current findings support for the hypothesis that in the presence of an adequate WM retention in the period prior to interference (revealed by the absence of differences between groups in the pre-interference period and by the increased power of theta in the post-interference period in accurate responses in MCI patients), the presence of interruption and its handling alters the ongoing activity of this frequency band, which results in the forgetting of the representations being held in WM.

Support for these results arises from findings revealing theta activity and memory accuracy reduction by means of memory load demands, which indicate the role of this frequency band in supporting memory abilities (Cummins et al., 2008).

In a similar manner, brain activity decreases have been frequently linked with reductions in cognitive performance and with advanced brain pathological states as accounts in dementia (Prvulovic et al., 2005; Kochan et al., 2010; Clement et al., 2012; see Dickerson and Sperling, 2008 for review). In this line, patients with reduced theta power in error trials were those with greater hippocampal atrophy, showing that as the disease progresses, there is also a depletion of the mechanisms that control cognition.

As described in the Experiment I, patients with MCI show difficulties to handle interference, likely due to deficits in inhibitory and in task-switching abilities. Interestingly, and supporting the current results, these alterations have been revealed to contribute to WM abilities when interference accounts during retention periods. The current experiment was focused on the effect of switching between two concurrent tasks (interruption-type interference) on memory retention abilities. In this line, the current results show that while maintaining sensory information and handling interruption in WM, brain oscillations in the theta range point to plan an essential role for successful memory retention and for forgetting of information in MCI patients.

**The role of alpha power in WM retention with interruption in MCI**

Our observations confirmed expectations regarding the presence of high alpha power values in the post interference period in MCI patients when comparing with controls. The fact that the current data were normalized with the TFR values regarding the no interference condition indicates that the increased alpha band is highlighted when there is an increase in the demands of the task (accounted by the presence of interference). Furthermore, patients with higher post-interference alpha values showed reduced task accuracy, and reduced hippocampal volume rates. These relations were not observed in the healthy group.

Altogether, in the line with results from the Experiment II, the increased alpha power observed in MCI patients during the post-interference period of the task does not indicate to be related with any functional process, whereas it seems to show an opened window to the underlying pathology in the brain.

Thus, as described in Experiment II, the presence of aberrant alpha power points to be related with underlying pathology in the brain, possibly showing decreased gabaergic inputs to the neurons, contributing to the observed hiper-excitacion of the activity of the brain. This hypothesis is again supported by the decreased performance level shown by the patients that revealed higher power in this frequency band.

Together, the presence of high alpha power values in the MCI group seems to reflect accumulation of pathology in the brain, which contributes to memory decline. Future studies evaluating the role of alpha oscillations in memory retention with and without interference would contribute to clarify this hypothesis.

# CHAPTER 5. Conclusions and future directons

## Conclusions

An overview of the results of the current three experiments allows concluding that forgetting in MCI patients is a complex process which depends on cognitive and neurophysiological variables. As exposed in Experiment 1, the presence of interference (both, distraction and interruption) during WM retention periods in an essential contributor to WM forgetting in aging, and especially in MCI patients. It is therefore conclusive that deficits in executive functions that manifest as a marked vulnerability to control external interference, contribute to one of the best known symptoms of the MCI clinical profile, namely, forgetting. Furthermore, this study aimed to show that the demands of the interference stimuli modulate forgetting, where interruption is the most disruptive to the memory retention abilities, again especially in MCI patients. Thus, the role of interference in memory, and more precisely the role of interruption, offers an important hallmark to further understand memory-related deficits in MCI. It therefore appears necessary to take into account how external stimuli impact memory in MCI pathology, whether for clinical practice, cognitive research, whether for everyday living activities.

Aiming to disentangle the brain neurophysiological mechanisms that support WM retention and forgetting, in the presence and absence of interference, the second and the third Experiments revealed, on one hand, that the activity in the theta frequency range is one of the oscillatory mechanisms responsible for WM retention and forgetting in MCI patients. Therefore, it is conclusive that increased oscillatory power of theta is necessary for successful WM retention in MCI patients, whereas its depletion (together with the increase of the alpha power) is responsible for WM forgetting after handling interruption in this population. In an additional manner, the

relation between theta power and hippocampal volume in MCI patients supports the hypothesis of the role of theta power increase as a compensatory mechanism in those patients with higher rates of hippocampal atrophy.

On the other hand, findings from the second and third Experiments showing increased power in the alpha band during WM retention, in the presence and absence of interruption, and showing a negative relation with task accuracy and with hippocampal volume in MCI patients, point to reflect underlying brain damage which contributes to reduction in the WM retention capacity of this population. In this sense, the neuronal over-excitation points to reflect over-excitation of the system due to the progressive loss of gabaergic neurons, induced by the progressive accumulation of the beta amyloid plaques in the MCI brain. Thus, it seems straightforward that the presence of aberrant alpha power could be established as a bio-sign of disease. The role of this hiper-excitability pattern is still a matter of debate. Nevertheless, if this hypothesis confirmed, potential pharmacological treatments, such as antiepileptic drugs, would be good candidates to prevent cognitive decline in this population.

Altogether, the current results indicate that the brain oscillatory activity of MCI patients underlying WM retention is characterized by a dual neurophysiological pattern, reflecting both compensatory and dysfunctional mechanisms.

The abovementioned assumptions may involve important implications in theories of forgetting in aging, as well as in understanding the neurophysiological mechanisms of the continuum to AD. From the cognitive theories of forgetting, it is now shown that interference is a decisive factor inducing forgetting in MCI patients. In this line, special attention should be taken to the role of theta in WM abilities in MCI patients, and importantly, special attention should be taken to alpha hyper-excitability which could help identifying patients with MCI at a great advantage for early clinical diagnosis of dementia. Thus, it is necessary to test whether those MCI patients converting to AD show, or not, this hyper-excitability pattern.

In sum, the main conclusions from the current three experiments are the following:

- **WM forgetting in MCI is influenced by vulnerability to handle external interference**.

- **This vulnerability depends on the demands of the interfering stimulus, being interruption the most disruptive to the memory retention process in MCI patients.**

- **The brain activity underlying WM retention in MCI patients indicate the presence of a dual oscillatory pattern, showing both compensatory and dysfunctional mechanisms**

- **Successful WM retention in MCI patients, in the presence and absence of interruption, is supported by increased power in the theta frequency range, with higher theta values shown by patients with greater hippocampal atrophy.**

- **WM forgetting by the presence of interruption is reflected by depletion of theta and over-activation of alpha power in MCI patients.**

- **Aberrant alpha activity during WM retention processes, in the presence and absence of interference, points to reflect brain pathology of the MCI brain**

# Future directions

Future studies should continue investigating the role of executive functions in the forgetting experienced by MCI patients. Additionally, future work should evaluate the effect of interference in memory across the continuum to AD, and study the relationships between its effect and the severity of the disease.

Furthermore, studies evaluating the brain activity patterns underlying WM retention and forgetting should evaluate correct and incorrect responses and vary in tasks demands (such as in memory load) on several clinical states across the AD spectrum. Such investigations will provide deeper comprehension of the role of brain oscillations underlying memory failures in this population, and will provide new perspectives for cognitive and pharmacological interventions.

Additionally, advances methodologies, such as connectivity analysis will allow studying the interdependence between the distributed regions in the brain that support WM retention and forgetting in the MCI population.

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