UNIVERSIDAD COMPLUTENSE DE MADRID
FACULTAD DE PSICOLOGÍA

TESIS DOCTORAL

Cognitive and neural mechanisms of episodic memory reactivation: from consolidation to retrieval

Mecanismos cognitivos y neurales de la reactivación de la memoria episódica: de la consolidación a la recuperación

MEMORIA PARA OPTAR AL GRADO DE DOCTORA

PRESENTADA POR

María del Carmen Martín-Buro García de Dionisio

DIRECTORES

Bernhard P. Staresina
Fernando Maestú Unturbe

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BAJO LA DIRECCIÓN DE LOS DOCTORES

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A doctoral thesis submitted by María del Carmen Martín-Buro García de Dionisio for partial fulfilment of the requirements for the degree of Doctor with International mention under the direction of Dr. Bernhard P. Staresina and Dr. Fernando Maestú at the Faculty of Psychology of the Complutense University of Madrid.

Madrid, 2019

A Emilio

A mis padres y hermanas

A todos los que alguna vez me han enseñado

To all those who have ever taught me

Contents

"The heart is hard to translate"
Florence and the Machine

Acknowledgements / Agradecimientos

I can tell that there have been two turning points in my research career. The most profound took place during my research stay at the University of Birmingham where I met one of my advisors, Bernhard Staresina. Not only has he been an extremely patient and generous mentor, but he has also been a role model of how science should be conducted and enjoyed. Even if I wrote this in my mother tongue, I would probably not find the words to express my gratitude for his careful guidance. I want to thank Bernhard for teaching me despite the distance, and more importantly, for waiting for me while I was learning. If I am independent in any research skill at the present time it is mainly because of him. I cannot overstate how honoured I am for the trust placed in me during these years, and how this made me grow.

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He compaginado este proyecto con mi trabajo como docente en el CES Cardenal Cisneros (adscrito a la UCM) y, durante el último año, también en la Universidad Rey Juan Carlos de Madrid. De esta forma, la

docencia, además de convertirse en mi pasión, ha sido mi medio de vida. Por ello, agradezco enormemente la oportunidad que me han brindado estas dos instituciones y todo el apoyo que recibido de mis compañeros (profesores y PAS).

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This doctoral thesis presents two studies conducted with the collaboration of Dr. Maria Wimber (University of Birmingham) and Dr. Richard Henson (MRC Cognition and Brain Science Unit, University of Cambridge). I am gratefully indebted for their valuable comments and assistance. I would also extend my thanks to the MRC Cognition and Brain Science Unit of the University of Cambridge for providing with the necessary technical support and equipment for data acquisition, and Dr. Maria Wimber and Dr. Bernhard Staresina for data collection.

Es muy difícil verse a uno mismo. Incluso frente al espejo somos incapaces de ver cómo se mueven nuestros ojos a pesar de que ciertamente los estemos moviendo. Lo más dramático es que el cerebro no registra lo que ocurre durante esos movimientos y, llamativamente, nuestra experiencia no es ni estática ni incompleta. Conocemos los mecanismos que tiene el cerebro para no caer en un abismo cada vez que nuestros ojos saltan de un sitio a otro, sin embargo, sigue siendo muy difícil "verse" a uno mismo. Estrujando los límites de la introspección uno puede llegar a conseguirlo, sin embargo, si nos detenemos ante esa imagen no tardaremos en darnos cuenta de que en muchas ocasiones ha sido la mirada que nos devolvían los demás, más que la mirada propia, la que nos ha permitido disponer de esa información. Al final, parece que uno se ve a sí mismo a través de los ojos de los demás. Yo he tenido la suerte de cruzarme con miradas desmesuradamente benevolentes que, seguramente, me han devuelto una versión más fuerte y capaz de mí misma.

Hay dos personas con las que he contraído una deuda que trasciende esta tesis doctoral. A Pilar Gallo y Juan Hermoso les debo la curiosidad

por las preguntas complejas. No solo me enseñaron Psicología, sino que me enseñaron a pensar sobre la Psicología del modo en que hoy lo hago. A Pilar le debo haberse dado cuenta de que me hacía preguntas relevantes mucho antes de darme cuenta yo misma. Gracias por haber alimentado y seguir alimentado esas preguntas, eres para mí ejemplo y fuente de inspiración. A Juan le debo mis primeras reflexiones sobre lo mental y la oportunidad de haber hecho de estas reflexiones mi sustento. Hubo un momento de mi vida en el que el estudio me salvó, y fue gracias a la forma que ambos tienen de transmitir el conocimiento.

My deepest thank to Rodi, Cati and Juan for creating a real home, for understanding me and helping me to learn and grow beyond science. Thanks for *taking a chance on me*. From the bottom of my heart, I do believe that I am a better person since I know you. Rodi, thank you for your limitless generosity and everyday happiness (I still miss it). Cati, thank you for being the music and the dance one always needs. Never lose that smile. Juan, thank you for showing me a little of your amazing world.

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De las experiencias a las que uno se aferra para mantener el espíritu fuerte me quedan las conversaciones y contemplaciones con Amaranta y Lucas. Además de una profunda conexión intelectual y emocional, les debo una experiencia que no he vuelto a tener: estudiar de forma inter-subjetiva, al más puro estilo Vygotsky. Guardo nuestras conversaciones y aquel cielo estrellado como un tesoro.

No puedo negar que parte del tiempo dedicado a esta tesis ha sido robado a mis amigas/o de siempre (las Brinsesas). Algunas de ellas me acompañan en la vida desde que tengo memoria, y entre todas hemos creado una auténtica familia. Gracias por ser un sitio donde poder ser una misma y al que siempre se quiere volver.

GRACIAS a mis padres y a mis hermanas. No hay nada que pueda decir que haga justicia al sentimiento de agradecimiento que siento hacia mis padres, quienes han hecho grandes sacrificios para que no nos falten oportunidades y para que nunca nos sintamos solas ante las adversidades.

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List of abbreviations

AAL	Automated Anatomical Labelling
AM	Associative memory
ANOVA	Analysis of Variance
BOLD	Blood-oxygen-level dependent
CA	Cornu Ammonis
CLS	Complementary learning systems
CPFm	Córtex prefrontal medial
CR	Correct rejection
EEG	Electroencephalography
ECG	Electrocardiogram
EOG	Electrooculogram
ERF	Event-related field
ERP	Event-related potential
fT	Femtotesla
HEOG	Horizontal electrooculograms
H.M.	Henry Molaison
HPI	Head position indicator
Hz	Hertz
iEEG	Intracranial electroencephalography

IM	Item memory
fMRI	Functional Magnetic Resonance Imaging
M/EEG	Magneto and Encephalography
MEG	Magnetoencephalography /Magnetoencefalografía
mPFC	Medial Prefrontal cortex
MRI	Magnetic Resonance Imaging
ms.	Milliseconds
MTL	Medial temporal lobe
MVPA	Multiavariate pattern analsyis
NMDA	N-methyl-D-aspartate
NREM	No rapid eyes movement (sleep)
lcmv	Linearly constrained minimum variance (beamforming)
LDA	Linear Discriminant Analysis
lMTL	Left medial temporal lobe
LTP	Long term potentiation
LTM	Lóbulo temporal medial
p	p value
PFC	Prefrontal cortex
PPC	Posterior parietal cortex
r	Pearson's rho
RMf	Resonancia magnética funcional
RT	Reaction time
s.	Seconds
SEM	Standard error of the mean
SSRs	Steady-state responses
SSVEPs	steady-state visual evoked potentials (SSVEPs)
SWRs	Sharp wave ripples
VEOG	Vertical Electrooculogram

List of figures

List of tables

Chapter 1

Summary and outline

Cognitive and neural mechanisms of episodic memory reactivation: from consolidation to retrieval

Summary

Introduction

Episodic memory is the result of highly dynamic processing. After encoding, the memory trace undergoes a set of transformations that range from the unconscious replay during waking rest periods to the full-blown reactivation that gives rise to our experience of recollection. The literature review reveals that, despite our knowledge of the neocortical-hippocampal circuits involved, their brain oscillatory mechanisms remain unclear.

Objective

The main goal of this doctoral thesis is to track episodic memory reactivation during consolidation and retrieval by means of its oscillatory signatures. Explicitly, we aim to unveil how their underlying neural mechanisms unfold over time and space to coordinate behaviour.

Experimental study I: Consolidation

Following the natural mnemonic processing, we first addressed the stage of consolidation. Systems consolidation refers to the set of post-encoding processes engaged in reorganising our long-term memories over distributed brain circuits. Depending on the age and the content of the memory trace, part of these processes rely on the hippocampus and the mPFC (Preston & Eichenbaum, 2013). This progressive memory transformation across time is proposed to be achieved by the offline reactivation or replay of the brain patterns generated during the initial experience (Buzsáki, 1989; Marr, 1971). Evidence in rodents has already demonstrated that this reactivation can occur spontaneously after learning during subsequent wakefulness periods (Carr, Jadhav, & Frank, 2011; Gardner & Moser, 2017). In humans, neuroimaging evidence has successfully shown awake reactivation based on the re-emergence of spatial patterns (Staresina, Alink, Kriegeskorte, & Henson, 2013). In parallel, electrophysiological studies have used cued-triggered paradigms and showed reactivation during wakefulness and sleep (Schreiner, Doeller, Jensen, Rasch, & Staudigl, 2018). Since this reactivation is artificially generated, it may differ from the spontaneous consolidation. To overcome this limitation, we[1] used MEG oscillatory entrainment on a paired associate memory paradigm to track reactivation during (uncued) waking rest periods immediately after the study phase. To further relate reactivation to subsequent memory performance we also manipulated the depth of processing (deep and shallow) during encoding (Craik & Lockhart, 1972). Our findings showed that offline periods produced the re-emergence of the entrained frequencies during resting periods. Specifically, a post-encoding power increase was found over the frontal sensors of the helmet and only for the deep encoding condition. The projection of this reactivation into source-space indicated engagement of the left mPFC, bilateral inferior frontal gyrus, and the MTL. Across participants, the reactivation of the entrained oscillatory patterns predicted the subsequent recollection. To our knowledge, this is the first

[1] For the sake of clarity and following the current guidelines of representative journals such as *Nature*, this thesis is written in active voice. The use of 'we' acknowledges the valuable commentaries of advisors and collaborators.

time that mPFC-MTL reactivation of recent memories is captured by the oscillatory patterns.

Experimental study II: Retrieval

At the stage of retrieval, our memories for past encounters can range from a vague feeling of familiarity to full-blown recollection of associated details. On the one hand, Electroencephalography (EEG) has shown that recollection-related signals unfold a few hundred milliseconds after familiarity and are hallmarked by sustained voltage deflections over left posterior sensors (Herron, 2007; Rugg and Curran, 2007; Mecklinger et al., 2016). However, sensor-based analyses only provide limited insights into the supporting brain networks. On the other hand, functional magnetic resonance imaging (fMRI) has revealed a consistent 'core recollection' network centred on posterior parietal and medial temporal lobe (MTL) regions (Hayama, Vilberg, & Rugg, 2012; Rugg & Vilberg, 2013). However, due to the relatively poor time resolution of fMRI, the temporal dynamics of these regions during retrieval remain largely unknown. In order to overcome these modality-specific limitations, we here used whole-head Magnetoencephalography (MEG) in a verbal episodic memory paradigm assessing item memory (IM; familiarity) and associative memory (AM; recollection). Intriguingly, the present study found that power decreases ('desynchronization') in the alpha frequency band (10-12 Hz) systematically track mnemonic outcomes in both time and space: AM showed a sustained alpha power decrease relative to IM from ~800 ms onward. Importantly, when projecting these alpha band patterns into source space, results revealed recollection effects in the 'core recollection network' emerging from fMRI studies, including posterior parietal cortex and hippocampus.

Conclusion

The experimental work conducted in this thesis is based on an updated review of our current knowledge on episodic memory, from foundational psychological concepts to recent models in the field of cognitive neuroscience. Overall, this thesis unveils the cognitive and neural

underpinnings of two expressions of episodic memory reactivation. First, it demonstrates that consolidation can be tracked by the spontaneous reactivation of oscillatory patterns over the mPFC-MTL circuit. This finding extends previous evidence about mPFC engagement on consolidation. However, it also challenges some models that proposed its engagement for remote memories. Methodologically, our results using oscillatory entrainment may open new venues to investigate cognitive operations during offline periods. With regard to recollection, our data suggest that alpha desynchronization constitutes a fundamental oscillatory mechanism revealing when and where our memories are retrieved. Since previous research on recognition found theta and gamma synchronization at earlier latencies and different topographies, our results raise the possibility of an interplay between different frequency bands during recognition that future studies could address.

The methodology and findings of this thesis have a direct impact on the current body of knowledge and contribute to addressing existing models and theories. An accurate analysis of different expressions of episodic memory reactivation enables us to value its impact and not to miss the opportunity to exploit it; either improving learning strategies, relieving recurrent traumatic memories or setting new targets of neuropsychological rehabilitation.

Outline of the thesis

This thesis contains six chapters. Chapter 1 comprises the summary in English and Spanish, and this overview. Chapter 2 reviews the main conceptual frameworks from the perspective of psychology and cognitive neuroscience regarding episodic memory. It also introduces the gaps in the knowledge and the problems addressed. Chapter 3 explains the purpose, the specific objectives and hypotheses for each experimental study, as well as the significance of this thesis. Chapters 4 and 5 expound the experimental studies. Each of these chapters comprises an introduction with the state-of-the-art review for each problem, along with the methodology, results, discussion and specific conclusions. Specifically, Chapter 4 includes evidence for awake reactivation linked to consolidation processes, and Chapter 5 presents the spatial and temporal

oscillatory dynamics of recollection. Finally, Chapter 6 discusses the implications, limitations and possible future lines of research derived from this work.

Mecanismos cognitivos y neurales de la reactivación de la memoria episódica: de la consolidación a la recuperación

Resumen

Introducción

La memoria episódica es el resultado de un procesamiento altamente dinámico. Tras la codificación, el recuerdo sufre una serie de transformaciones que abarcan desde la reactivación (*replay*) inconsciente durante los periodos de reposo en vigilia, hasta la reactivación íntegra que da lugar a nuestra experiencia subjetiva de 'recordar' (vs. reconocer). A pesar de que conocemos las regiones cerebrales implicadas, sus mecanismos neurales oscilatorios siguen sin conocerse adecuadamente.

Objetivo

El objetivo principal de esta tesis es rastrear la reactivación de la memoria episódica durante la consolidación y la recuperación a través de sus perfiles de actividad oscilatoria. En concreto, a partir de registros de Magnetoencefalografía (MEG) con participantes sanos, se pretende desvelar cómo se despliegan los mecanismos neurales subyacentes en el tiempo y el espacio para coordinar el comportamiento.

Estudio experimental I: Consolidación

Siguiendo el curso temporal del procesamiento mnemónico, en primer lugar abordamos[2] la etapa de la consolidación. La consolidación de sistemas hace referencia al conjunto de procesos post-codificación que permiten reorganizar nuestros recuerdos a largo plazo en circuitos cerebrales distribuidos. En función de la antigüedad y el contenido del recuerdo, parte de estos procesos dependen del hipocampo y del córtex prefrontal medial (PFCm) (Preston & Eichenbaum, 2013). La transformación progresiva del recuerdo con el tiempo se consigue gracias a la reactivación *offline* de los patrones cerebrales generados durante la experiencia inicial (Buzsáki, 1989; Marr, 1971). La evidencia en roedores ya ha demostrado que esta reactivación puede ocurrir espontáneamente tras el aprendizaje durante la vigilia subsiguiente (Carr et al., 2011; Gardner & Moser, 2017). Sin embargo, la evidencia electrofisiológica en humanos está limitada a la reactivación generada artificialmente mediante el uso de claves (Schreiner et al., 2018), por lo tanto, podría diferir de la consolidación que se produce de forma espontánea. Para superar esta limitación, hemos utilizado la inducción oscilatoria (*oscillatory entrainment*) con MEG y un paradigma de memoria con pares asociados de palabras para capturar la reactivación (sin claves) durante periodos de vigilia inmediatamente después de la fase de estudio. Para relacionar la reactivación con el recuerdo, también se manipuló la profundidad de procesamiento (profunda y superficial) durante la codificación (Craik & Lockhart, 1972). Nuestros hallazgos muestran que las frecuencias utilizadas durante la inducción re-emergen de nuevo durante los periodos de reposo (*offline*). Concretamente, encontramos un aumento de la potencia post-codificación en los sensores frontales, pero solamente para la condición de codificación profunda. La proyección de esta reactivación en el espacio de fuentes revela la participación del PFCm izquierdo, giro frontal inferior bilateral y regiones del lóbulo temporal medial (LTM), que correlaciona con el recuerdo posterior. Dada la evidencia actual, esta es la primera vez que la reactivación en el

[2] En aras de mostrar la máxima claridad posible y siguiendo las recomendaciones de revistas representativas como *Nature*, en ocasiones se utilizará la voz activa. El uso de la tercera persona del plural reconoce los valiosos comentarios de supervisores y colaboradores.

circuito PFCm-LTM de recuerdos recientes es capturado a través de sus patrones oscilatorios.

Estudio experimental II: Recuperación

En la etapa de recuperación, nuestros recuerdos sobre eventos pasados abarcan desde el vago sentimiento de familiaridad hasta el recuerdo íntegro de los detalles asociados. Por un lado, los estudios con Electroencefalografía muestran que las señales del recuerdo emergen cientos de milisegundos después de las de familiaridad en sensores posteriores izquierdos (Herron, 2007; Rugg and Curran, 2007; Mecklinger et al., 2016). Sin embargo, los análisis en el espacio de sensores nos permiten un acceso muy limitado a las redes cerebrales subyacentes. Por otro lado, la resonancia magnética funcional (RMf) revela sistemáticamente una 'red básica de recuerdo' centrada en regiones parietales posteriores y del LTM (Hayama et al., 2012; Rugg & Vilberg, 2013). Dada la limitada resolución temporal de la RMf, aún desconocemos la dinámica temporal de esta red durante la recuperación. Para superar estas limitaciones específicas de cada modalidad, hemos utilizados un registro de MEG con una tarea de memoria episódica verbal que permite evaluar la memoria del ítem (MI, familiaridad) y la memoria asociativa (MA, recuerdo). Llamativamente, nuestros datos revelan una disminución de la potencia (desincronización) del ritmo alfa (10-12Hz) que rastrea sistemáticamente el tipo de reconocimiento tanto en el tiempo como en el espacio: la MA muestra una disminución sostenida de la potencia de alfa relativa a la MI a partir de los 800ms en adelante. La proyección de estos patrones del ritmo alfa al espacio de fuentes muestra la participación de la 'red básica de recuerdo', tradicionalmente identificada con RMf, incluyendo el córtex parietal posterior y el hipocampo.

Conclusión

El trabajo experimental de esta tesis se fundamenta en una revisión actualizada de nuestro conocimiento actual sobre la memoria episódica, partiendo de los conceptos fundamentales propuestos por la psicología,

hasta llegar a los modelos más recientes de la neurociencia cognitiva. En conjunto, esta tesis desvela los fundamentos cognitivos y neurales de dos expresiones de la reactivación de la memoria episódica. En primer lugar, se demuestra que la consolidación puede ser rastreada a través de la reactivación de patrones oscilatorios en el circuito PFCm-LTM. Este hallazgo amplía la evidencia previa sobre la participación del PFCm en la consolidación. Sin embargo, también supone un reto para aquellos modelos que destacan su participación en recuerdos remotos. Metodológicamente, los resultados derivados de la aplicación de la inducción oscilatoria pueden abrir nuevas vías para la investigación de las actividades cognitivas durante periodos *offline*. Por lo que respecta a la recuperación, nuestros datos sugieren que la desincronización del ritmo alfa constituye un mecanismo oscilatorio fundamental que revela cuándo y dónde se recuperan los recuerdos. Dado que la investigación previa con paradigmas de reconocimiento muestra una sincronización en las bandas theta y gamma en latencias más tempranas y topografías diferentes, nuestros resultados apuntan a una posible interacción entre diferentes bandas de frecuencia durante el reconocimiento que podría ser investigada en futuros estudios.

La metodología y los hallazgos descritos en esta tesis tienen un impacto directo sobre nuestro conocimiento actual y contribuyen a la evaluación de los modelos y teorías vigentes. Realizar un análisis adecuado de las diferentes expresiones de la reactivación de la memoria episódica, nos permite valorar su impacto y no malgastar la oportunidad para explotarlo en el futuro, ya sea mejorando las estrategias de aprendizaje, aliviando recuerdos traumáticos recurrentes o estableciendo nuevos objetivos en la rehabilitación neuropsicológica.

Estructura de la tesis

Esta tesis está compuesta por seis capítulos. El Capítulo 1 incluye un resumen en inglés y en español, y esta presentación esquemática. El Capítulo 2 revisa los principales marcos conceptuales desde la perspectiva de la psicología y la neurociencia cognitiva. También introduce las lagunas que existen en nuestro conocimiento y los problemas abordados. En el Capítulo 3 se explica el propósito, los objetivos específicos y las hipótesis de cada estudio experimental, así como el sentido de la tesis.

Los Capítulos 4 y 5 exponen los estudios experimentales. Cada uno de estos capítulos contiene una introducción sobre el estado actual de cada problema, junto con la metodología, los resultados, la discusión y las conclusiones específicas. En concreto, el Capítulo 4 incluye evidencia sobre la reactivación en vigilia vinculada a los procesos de consolidación, y el Capítulo 5 la dinámica espacial y temporal de las oscilaciones cerebrales durante la recuperación (recuerdo). Finalmente, en el Capítulo 6 se discutirán las implicaciones, limitaciones y posibles líneas de investigación futuras derivadas de este trabajo.

Chapter 2

Episodic memory: a brief review from psychology and cognitive neuroscience

1. Introduction

On the first pages of the foundational book *Principles of Psychology*, William James encapsulated in few words what later on has crystallised in a plethora of papers, symposia and handbooks: the scope of memory research from Psychological science.

> For why should this absolute god-given Faculty retain so much better the events of yesterday than those of last year, and, best of all, those of an hour ago? Why, again, in old age should its grasp of childhood's events seem firmest? Why should illness and exhaustion enfeeble it? Why should repeating an experience strengthen our recollection of it? […] Such peculiarities seem quite fantastic; and might, for aught we can see *a priori*, be the precise opposites of what they are. Evidently, then, *the faculty does not exist absolutely, but works under conditions; and the quest of the conditions* becomes the psychologist's most interesting task. (James, 1890 p.2-3)

The reason for this fruitful work attempting to solve some of these questions should be evident: memory is at the core of our cognition. Thanks to our memory, one can mentally walk backwards and re-live feelings and sensations from the past with an incredible amount of detail. These memories range from the vision of oneself as a carefree child running with wounds in the knees, to the recall of the face of a friend telling a joke during a dinner a few days ago. Although we treasure our more intimate memories, the relevance of memory goes further than this subjective experience because its well-functioning determines many of our daily behaviours. For instance, holding a conversation, recognising familiar faces –including our own face– or understanding these words strongly rely on the memory contents and mechanisms. Precisely, how the neural and cognitive system gets by working under some of the

conditions that James brightly highlighted is the leitmotiv of the present thesis.

In parallel to the publication of James' work, two striking discoveries set the foundations of subsequent neuroscience developments. Santiago Ramón y Cajal was shaping the neuron doctrine (Cajal, 1894) which later deserved the Nobel Prize of Medicine and has emerged as the central tenet of modern neuroscience. Cajal's observations culminated in the conception of neurons as single discrete units that transmit the impulse from the dendrites to the axon across the synapse. This ground-breaking portrayal of the neuronal communication is at the background of our current attempts to understand how populations of neurons give rise to brain oscillations.

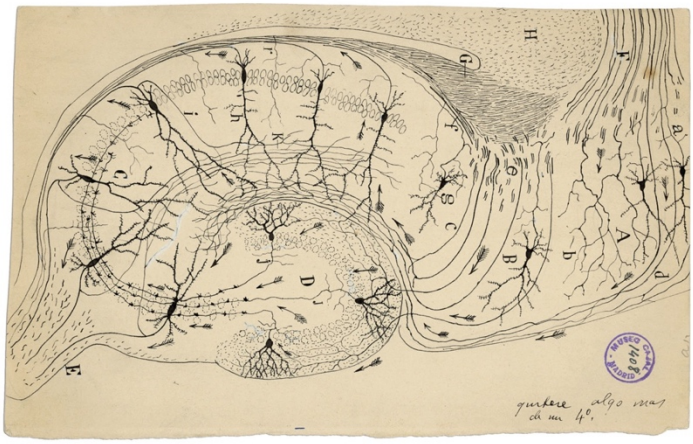

Figure 1. Cajal's drawing of the hippocampus showing neurons as discrete cells. Notice that the arrows depict the complex hippocampal intrinsic circuitry (Source: Cajal Institute)

Few years before, Adolf Beck had described spontaneous oscillations, evoked potentials and the desynchronization of brain waves following stimulation (Beck, 1890). His extensive work with animals served as breeding ground (Coenen, Fine, & Zayachkivska, 2014) for the noteworthy first electroencephalography (EEG) recording of the human alpha rhythm (8-13Hz) by Hans Berger (Berger, 1934).

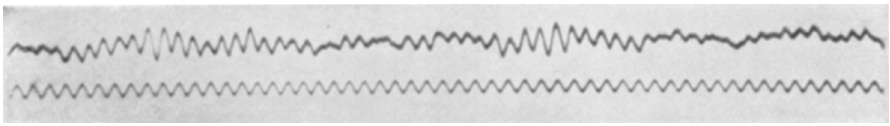

Figure 2. First human EEG alpha rhythm recorded by Hans Berger (Source: Wikimedia Commons).

Neuroscience and psychology would meet again in the figure of the distinguished neuropsychologist Alexander Luria. It is remarkable how his intuitions about the neurocognitive organisation envisioned modern concepts of the field of cognitive neuroscience such as functional segregation and integration:

> Mental functions, as complex functional systems, cannot be localized in narrow zones of the cortex or in isolated cell groups, but must be organized in systems of concertedly working zones, each of which performs its role in complex functional systems, and which may be located in completely different and often distant areas (Luria, 1973, p.31)

According to Luria, the study of higher cognitive functions should first focus on unveiling the functional role of each zone and how it contributes to the complex mental activity. Worthy of note is that his advanced understanding was not too far from current neuroscience proposals. For example, he described a functional unit for obtaining, processing and storing incoming information based on the activity of occipital, parietal and temporal regions (Luria, 1973). As it will be commented in the present thesis, these regions appear systematically in electrophysiology and neuroimaging studies underlying memory processes (*see Electrophysiological signatures of episodic memory*)

Cognitive neuroscience is usually defined as the intersection between psychology and neuroscience that aims to study the neural substrates of mental processes (Milner, Squire, & Kandel, 1998). Some cognitive psychologists and philosophers have raised the question of whether the study of the brain has contributed to psychological theories (Coltheart, 2006) or will ever do it (Fodor, 1999), while others claim for the view that brain research can constrain cognitive theories (Cooper & Shallice, 2011; Henson, 2006; Ruz, 2006). This is a huge debate that falls outside the scope of the present work, but it should be pointed out that this thesis is focused on seeking some conclusions about the meaning of the neural

organisation of memory processing. Undeniably, much of the literature that is revised hereunder comprises neuroscientific evidence that radically changed our conception of human memory and the direction of subsequent memory research, e.g. our understanding of the functional architecture of human memory would not have been the same without Brenda Milner's ground-breaking work on the case H.M. (Scoville & Milner, 1957). From this example among others can be distilled the consideration that working both at the brain and the psychological level may increase the explanatory power (Marshall, 2009) for addressing the complexity of human memory.

The recent years have seen a massive growth of episodic memory research from the perspective of cognitive neuroscience, so before considering the particular gaps of knowledge that this thesis will attempt to fill (*see The knowledge gap*), we will tour the backbone of our understanding of episodic memory from its foundational concepts to the novel proposals. With this aim, this chapter is organised as follows: the first section will give a definition of episodic memory in contrast to other memory systems; the second section will examine the main cognitive and neurobiological models with a particular emphasis on those questions addressed in this thesis; and the third section will detail the already known neural signatures of episodic memory to later finish with an outlining of the missing pieces that motivate the present work. The following sections may thus serve as background information to contextualise the experimental work and the main implications of the results. That said, it is important to note that the Introduction section of each experimental study (*see Chapters 4 and 5*) will offer the state-of-the-art review for our specific research questions.

2. Definition of episodic memory

The neuropsychologist Brenda Milner used to take the night train from Montreal to evaluate a patient who had undergone a bilateral medial temporal lobectomy that resulted in severe memory impairment. He was known as patient H.M. to preserve his privacy, and his evaluation was part of her PhD research in collaboration with Donald Hebb and Wilder Penfield (Milner et al., 1998). Thinking on H.M's anterograde amnesia, i.e.: the inability to create new memories, one can imagine Milner

introducing herself in every testing session, explaining, again and again, the experimental procedures, looking in the eyes of someone that never, ever recognised her no matter how many times they had previously met. These were only some of the devastating effects of the memory loss suffered by patient H.M. (Henry Molaison), after the surgery. What is difficult to imagine is whether Milner was aware of the dramatic shift that her findings were about to produce in the comprehension of human memory. She described how Henry Molaison was able to learn motor skills that improve with practice, although he had no recollection of having learnt them (Scoville & Milner, 1957). In other words, this dissociation provided evidence for multiple memory systems (Milner et al., 1998; Squire & Zola, 1996): *Declarative memory*, the capacity to consciously recall facts and events; and *Non declarative memory*, a heterogeneous group of capacities such as visuomotor skills, habits and other learning abilities that are expressed through performance without conscious access.

A critical distinction within the Declarative memory system was introduced by Endel Tulving (Tulving, 1972) with the concept of *'episodic memory'*. Although our declarative memories are composed of knowledge for facts and personal experiences, only the latter conserve the spatiotemporal details that enable us to re-experience and relive past events. For instance, the word 'Madrid' may trigger two different kinds of memories: first, you might tell that it is the capital of Spain, and this is just a semantic memory because no contextual detail arises. Second, you might see yourself in the terrace of a tapas bar that summer in Madrid in which your skin was totally red because you forgot to wear sunscreen. This remarkable ability to perform a mental time travel and recollect what, when and where something happens is one of the hallmarks of episodic memory and clearly distinguishes it from factual knowledge or *semantic memory* (Tulving, 2002).

Since the pioneering work of Hermann Ebbinghaus (Ebbinghaus, 1885), experimental psychology has perfected episodic memory measurements in laboratory conditions. In general, participants study a list of items, typically words or pictures. Sometimes they can use their own strategies whereas in other cases they are asked to follow specific instructions. Each of these items is considered an episode for which retrieval is requested after a variable delay period. Retrieval can be

achieved in several ways (Hockley, 2008; Stern & Hasselmo, 2009): (i) requesting to recall any item of the previous list (*free recall*); (ii) presenting a cue related to the information being remembered (*cued-recall*); (iii) presenting the previously studied items mixed with a set of new items, and asking the participant to decide whether is an old or a new item (*recognition memory*). These experimental procedures mirror episodic memory in our daily life, and the success depends on the ability of the participant to encode and later re-establish the spatiotemporal context in which that item was previously experienced.

Behavioural studies have contributed to our current understanding of episodic memory in such a crucial way that we already have well-defined procedures to dissect every stage of memory and manipulate determinant variables that affect memory performance. This body of knowledge can be exploited now thanks to electrophysiological and neuroimaging techniques, revealing some aspects of episodic memory that have remained opaque to behavioural measurements.

3. Cognitive and neurobiological models of episodic memory

Over the past years, cognitive neuroscience research has focused on disentangling the processes that occur at the time of encoding and later retrieval. These two processes correspond to the moment we first encounter an object, person or place so that we create a memory trace and the subsequent ability to access to it. However, each retrieved memory is not the result of these two processes only and, once the experience is encoded, the resulting memory trace is fragile and needs consolidation to become more durable and stable (Dudai, 2004; Frankland & Bontempi, 2005). Then, it may be thought that the persistence and accessibility of a memory are determined by encoding and consolidation processes; however, episodic memory seems to be more dynamic. The process of retrieval demands the reactivation of contextual details that were present at the moment of encoding. Moreover, when a memory trace is reactivated it becomes fragile again and needs to be reconsolidated (Dudai & Eisenberg, 2004; Nadel & Land, 2000; Nadel, Hupbach, Gomez, & Newman-Smith, 2012). It follows that the fate of a memory

trace is not solely determined by encoding and it seems that its reactivation, either during consolidation or retrieval, plays an essential role in episodic memory.

The question of how memory unfolds over encoding, consolidation, and retrieval has been addressed in cognitive and neurobiological models. Thus, the aim of this section is offering an overview of the fundamental theoretical models that guide the present thesis in every step of the mnemonic processing.

3.1. Encoding

The view of memory as a result of a dynamic process was one of the main contributions of *the levels of processing framework* proposed by Craik and Lockhart (Craik & Lockhart, 1972). This framework went further than the conceptualisation of a memory trace as a copy of the experience and proposed that the cognitive system applies a series of transformations or processing operations to the incoming information that results in the storage of the event. On this basis, the levels of processing framework paid much attention to the stage of encoding and described one of the most robust memory manipulations that can be found in the literature (Baddeley, Eysenck, & Anderson, 2009): the depth or levels of processing. This framework proposed that the incoming information can be analysed on a progression from *shallow* to *deep* analysis that determines the success of the encoding process and, hence, the quality and persistence of the memory trace. Shallow encoding corresponds to a perceptual analysis based on the physical or sensory features such as colour or size, whereas deep encoding entails the extraction of meaning and the connection of the event with previously stored information (Craik & Lockhart, 1972). A standard instruction to induce shallow processing is asking the participant to count the number of letters of a word or whether it is written in capital letters or not. In the case of deep encoding, it is usual to ask if a word can be integrated into a sentence or if a certain combination of items is plausible or implausible (Baddeley et al., 2009; Ruiz-Vargas, 2010).

At the neurobiological level, theoretical and computational accounts (Lisman, 1999; Marr, 1971; Norman & O'Reilly, 2003; Rolls, 1996; Shastri, 2002; Teyler & Rudy, 2007) agree upon the crucial role of the

medial temporal lobe (MTL) –particularly the *hippocampus*– in episodic memory formation (Purves et al., 2004). The MTL is an anatomical system that comprises a set of areas known as hippocampal formation (Insausti & Amaral, 2012): hippocampus (CA fields), dentate gyrus, subiculum, entorhinal cortex; and adjacent areas like perirhinal and parahippocampal cortex (Squire, Stark, & Clark, 2004).

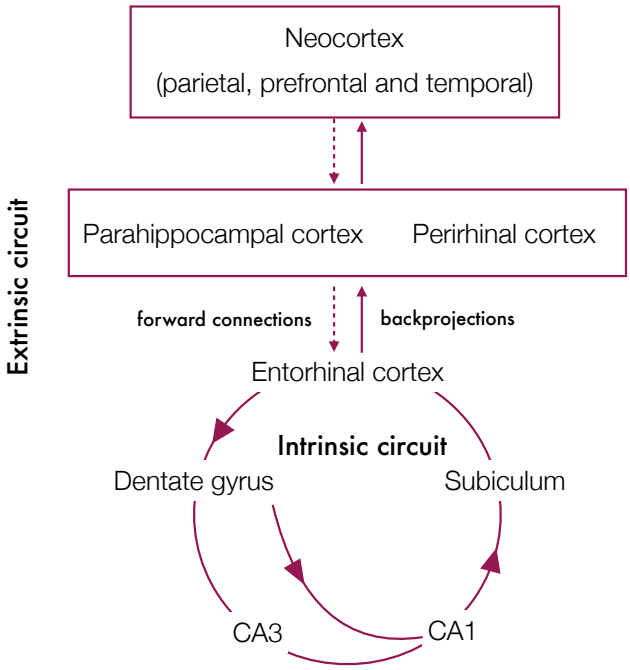

Figure 3. Hippocampal intrinsic and extrinsic circuits (adapted from Rolls, 2016)

One of the main features of the hippocampal formation is its complex and particular circuitry (Andersen, Morris, Amaral, Bliss, & O' Keefe, 2006). In general, neocortical regions circuits are reciprocal; however, this is not the case for many of the connections within the hippocampal formation (Andersen et al., 2006). In brief, hippocampal connectivity is twofold (*Figure 3*): intrinsic and extrinsic (Insausti & Amaral, 2012). For convention, the beginning of the intrinsic circuit may be considered the entorhinal cortex. The region provides the majority of the inputs to the dentate gyrus and also projects to CA1. Then, the granulate cells of the dentate gyrus project to CA3 via the mossy fibres and in turn, CA3

pyramidal neurons reach CA1 via Shaffer collaterals. The end of this intrinsic circuit would be the projections of CA1 and subiculum to the deep layers of the entorhinal cortex. As it will be explained in the upcoming sections, these hippocampal circuits constraint the nature of the episodic memory representations (sparse and pattern-separated, *see Encoding* section).

The extrinsic circuit may also start at the entorhinal cortex which can be considered a hub within the hippocampal network since it receives the most prominent neocortical projections and it also backprojects via parahippocampal and perirhinal cortex to prefrontal, parietal and temporal regions (Andersen et al., 2006; Norman & O'Reilly, 2003; Rolls, 2016). From this thesis will be derived that these cross-regional networks are critical to support memory processes during encoding, consolidation and retrieval.

An influential theory about how this hippocampus-neocortical dialogue coordinates episodic memory is the *hippocampal indexing theory* (Teyler & DiScenna, 1986; Teyler & Rudy, 2007). This theory claims that the individual features –the content– of a particular experience activate a set of neocortical modules. How is this short-lived experience turned into a memory trace? This pattern of neocortical activity is projected to a set of hippocampal neurons which plasticity properties allow to bind and encode the spatiotemporal patterns supported by the neocortex during the particular experience (*Figure 4A*). In other words, the memory trace is understood as a hippocampal *'index'* of the location and timing of the co-activated neocortical synapses. Therefore, the hippocampus would not contain the experience per se but a sort of map to access its content.

This conception of memory representation also determines how the process of retrieval unfolds. When a cue or a piece of the previous event appears, it activates a subset of the original neocortical pattern (*Figure 4B*). This partial pattern acts as input to the hippocampal neurons that were active during the encoding. Then, thanks to its indexing function, hippocampal backprojections (*Figure 3*) allow to activate the complete neocortical pattern yielding the reinstatement and retrieval of the initial experience (*Figure 4C*). Indeed, a recent optogenetic study has shown that direct stimulation of the hippocampal neurons that were active during encoding of a contextual fear conditioning can induce the learnt behaviour, i.e.: freezing (Liu et al., 2012).

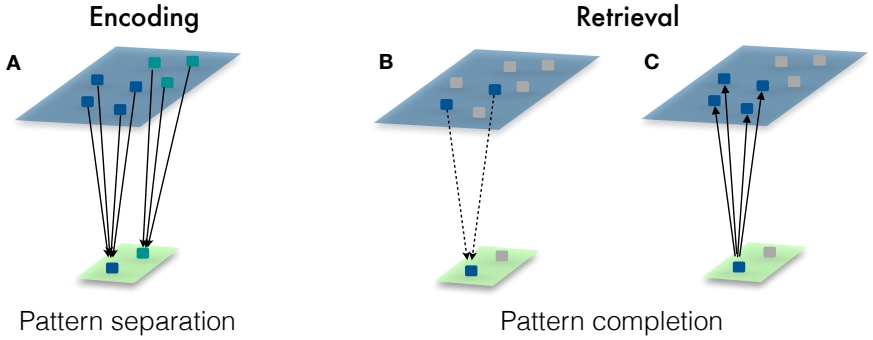

Figure 4. Hippocampal indexing theory (adapted from Teyler & Rudy, 2007). (A) During encoding, the hippocampus binds the co-activated neocortical pattern and ensures the uniqueness of the memory trace. (B) During retrieval, the partial activation of the neocortical pattern after a cue presentation triggers pattern completion (C) Hippocampal backprojections enable the re-establishment (retrieval) of the entire representation.

The functioning of the index strongly relies on the physiological properties of the hippocampus. First, from the circuits described above is assumed that the hippocampus is reciprocally connected to neocortical regions. Second, the creation of an index during encoding demands a mechanism that supports fast changes (Teyler & Rudy, 2007). These ideas have also been worked by the *complementary learning systems* (CLS) framework (McClelland, McNaughton, & O'Reilly, 1995; Norman & O'Reilly, 2003) and similar computational models (Marr, 1971; Rolls, 2016) to explain the contributions of the hippocampus and the neocortical regions to episodic memory. The central tenet is that there are two learning systems: a fast system in charge of learning specific events supported by the hippocampus, and a slow system to learn statistical regularities of the environment supported by the neocortex. But, how are these claims are implemented during encoding? One of the fundamental features of episodic memory is the ability to store a single and unique experience associated with when, where and what happened (Tulving, 2002). This uniqueness is achieved by creating distinct representations for the patterns of cortical activity (Norman, 2010) underpinned by the particular properties of the hippocampal circuitry (*see Figure 3*) (Rolls, 2016). In this line, the communication between the dentate gyrus and CA3 through the mossy fibre pathway which may result in separated representations (Rolls, 1996). Evidence for this idea is the fact that the

inactivation of the mossy fibres in mice has resulted in an impairment of encoding but neither consolidation nor retrieval (Lassalle, Bataille, & Halley, 2000). On the other hand, whereas pattern separation in the hippocampus ensures the uniqueness of the representation without suffering interference, the neocortex works with overlapping representations of different episodes to gradually extract the shared structure of the environment, i.e. semantic knowledge (Norman, 2010).

3.2. Consolidation

The dramatic memory impairment suffered by patient H.M. went further than his anterograde amnesia because the bilateral MTL resection also caused significant retrograde amnesia (Scoville & Milner, 1957), i.e.: a loss of recent memory or the inability to retrieve events encoded before the lesion. This impairment was circumscribed around the last 2-10 years before the surgery (Milner, Corkin, & Teuber, 1968). That is why, H.M.'s retrograde amnesia can be seen as neuropsychological evidence for the consolidation process first defined by Müller and Pilzecker (McGaugh, 2000). In a set of experiments, they observed the now well-known effect of the retroactive interference that happens when newly learned material interferes with previously stored information. Based on this phenomenon, they proposed that memories are not immediately fixed arguing that there is a period after encoding in which they are vulnerable (Lechner, Squire, & Byrne, 1999). Thus, *consolidation* refers to the progressive post-encoding stabilisation of long-term memory (Dudai, 2004). From this definition three relevant ideas can be distilled for experiment designing: (i) it is a time-dependent process; (ii) during the stabilisation time, recently encoded memories are fragile and sensitive to disrupting factors, and (iii) the result should be a more durable and resistant memory trace that might be tracked in subsequent retrieval.

This transformation of long-term memory over time and its neurobiological underpinnings have been studied under two not precluding concepts. On the one hand, *synaptic consolidation* refers to the earlier local stabilisation supported by the first molecular and cellular changes. And on the other hand, *systems consolidation* denotes the reorganisation of memory representations across brain circuits that can

last days, months or even years (Dudai, Karni, & Born, 2015). The temporal gradients of retrograde amnesia reveal the dynamic nature of memory representations and its gradual shift as time goes by.

Based on retrograde amnesia patients, initial proposals (Milner et al., 1998; Zola-Morgan & Squire, 1990) –also known as *standard consolidation theories*– suggested that MTL structures are necessary for episodic memory only until consolidation process ends. The MTL is viewed as a temporary binding system of the different neocortical modules. Over time, a direct connection between the discrete neocortical modules is gradually established, and the neocortex somehow assumes the function of MTL structures; as a result, consolidated episodic memories are not MTL-dependent anymore (Frankland & Bontempi, 2005; Nadel et al., 2012). However, the concept of consolidation has evolved, and this notion has been substituted by alternative theories (Moscovitch, Cabeza, Winocur, & Nadel, 2016). For example, the *multiple memory trace theory* (Nadel & Moscovitch, 1997) and its successive developments (Winocur, Moscovitch, & Bontempi, 2010) posit that as far as the memory contains contextual details, it will be hippocampal-dependent. These proposals claim that the memory trace is re-encoded each time is retrieved and, as time goes by, a gist memory or schematic version of the original episode with fewer contextual details is retained in the neocortex (Winocur et al., 2010). Building on the CLS model, since hippocampal and neocortical systems have different computational principles, the nature of the consolidated memory cannot be the same as the initial hippocampal-dependent representation. Rather than a transference of information, consolidation seems to be the creation of a distributed version in the neocortex of what the hippocampus was originally supporting (O'Reilly, Bhattacharyya, Howard, & Ketz, 2014).

In addition, recent studies have unveiled that the consolidation process is not homogeneous and may unfold differently in function of the incoming information and the prior schematic knowledge (Durrant, Cairney, McDermott, & Lewis, 2015; Tse et al., 2007; Wang & Morris, 2010). The boosting effect of schemas on episodic memory in humans has been systematically described during the last two decades (Bransford & Johnson, 1972), but recently, the medial prefrontal cortex (mPFC) has emerged as a critical structure that modulates episodic memory processes in function of the congruency of the information (Van Kesteren, Ruiter,

Fernández, & Henson, 2012). In this line, consolidation can be achieved by two routes: a fast route if the incoming information is congruent with prior knowledge –mental schemas–; or a slower route if it happens to be new information with no available mental schema. Compelling evidence came from studies with rats in which quick schema-dependent consolidation was related to changes in the gene expression in the mPFC (Tse et al., 2011). Besides, the pharmacological blockade of mPFC route (Tse et al., 2011), prevented rapid consolidation of new information and retrieval of remote consolidated memories. In other words, mPFC is necessary to consolidate new congruent information but also to sustain remote memories that are less hippocampus-dependent. This finding challenges somehow CLS proposals of hippocampal fast learning versus neocortical slow learning, so an exciting niche of research might have been opened.

Finally, one might ask how this transformation is achieved at the neural level? It has been demonstrated that the brain is highly active even when it is not engaged on a task (Raichle, 2015). A well-suited neural mechanism to underlie memory consolidation is the reactivation or replay of the hippocampal-neocortical interactions during *post-learning offline periods* (Dudai et al., 2015; Frankland & Bontempi, 2005). For instance, it has been found that during sleep there is a *reactivation* of the hippocampal representations during sharp wave ripples (SWRs) with further propagation to entorhinal and prefrontal cortex (Rasch & Born, 2013). Similar findings with immobile rodents showed that the place cells exhibit the same sequential activation that was displayed when they were moving and learning a path (Carr et al., 2011; Gardner & Moser, 2017). Moreover, the relevance of reactivation is also noted by its impact on behaviour in humans, as pointed by the fact that the presentation of a cue during slow-wave sleep can enhance subsequent performance (Rasch, Büchel, Gais, & Born, 2007). However, it remains elusive how spontaneous reactivation during waking rest happens in humans, what triggers this reactivation and how we can accurately track the feature-specific reactivation of an episode in the human brain.

3.3. Retrieval

Episodic retrieval is the result of a set of processes (Rugg & Henson, 2003) by which a retrieval cue (external- or internally generated) elicits the reconstruction of the prior experience (Rugg & Wilding, 2000). The complexity of episodic retrieval has been a major focus of interest among psychology and neuroscience, ranging from the very initial interaction between the cue and the memory representation, termed '*ecphory*' (Tulving, 1984) to the numerous factors and pre- and post-retrieval processes engaged during the retrieval attempt. Introspectively, retrieval allows us to mentally travel back in time and meet the challenge of whether an object, person or place has been previously encountered or not. However, retrieval phenomenology usually goes further than this initial vague feeling of *familiarity*, resulting in vivid and detailed memories. This remarkable ability to recollect content-rich memories with access to specific contextual details of the previous encounter is the result of relational or *associative memory* processes (Eichenbaum, Yonelinas, & Ranganath, 2007; Mayes, Montaldi, & Migo, 2007), also termed *recollection-based memory* (Yonelinas, 2002). This experience of retrieval differentiates itself from familiarity-based recognition by which it is possible to make an old/new decision but without remembering any detail of the previous experience.

During the last decades, much research has been conducted to study these two different expressions of recognition memory (for a review see Yonelinas, 2002). Psychology and cognitive neuroscience researchers have been involved in an intense debate regarding the nature of familiarity- and recollection-based recognition, and whether they imply same or independent processes (for a review see, Eichenbaum et al., 2007). On the one hand, some researchers claim that the difference between these two expressions of memory is quantitative, namely, they are not due to different processes and the observed differences are led by confidence (Dunn, 2004) or strength (Squire, Wixted, & Clark, 2007). In contrast, other view posits that familiarity and recollection involve qualitatively different processes (Rugg & Yonelinas, 2003; Yonelinas, 2002), relying on behavioural, neuropsychological and cognitive neuroscience dissociations (Aggleton & Brown, 2006; Yonelinas, Aly, Wang, & Koen, 2010). This last view –*dual-process theory*– found strong

support on the functional dissociation between different regions of the MTL. Backed by neuropsychological and animal evidence, this theory points toward the essential role of the hippocampus for recollection but not familiarity. This is in good agreement with the CLS framework (Norman, 2010; Norman & O'Reilly, 2003) previously commented in the present chapter when referring to the neurally inspired models of encoding. Concisely, the problem of creating a unique and non-overlapping memory representation during encoding was handled by pattern separation in the hippocampus (Norman, 2010; Rolls, 2016). Next, at the moment of retrieval, a cue or fragment of the previous experience activates the sparse representation in the hippocampus leading to the reinstatement of the original hippocampus-neocortical pattern. Mechanistically, when a cue is provided, CA3 hippocampal system reactivates via CA1 neocortical areas that were active during the original memory formation (Rolls, 2016). Promising results, such as the cued recall impairment found when NMDA receptor gene is ablated in a CA3 region, might support the causal role of pattern completion during retrieval (Nakazawa et al., 2002). It is argued that this is achieved thanks to the capability of the hippocampus for pattern completion through its backprojections (*see Figure 3*) to the neocortex (Rolls, 2016). In line with dual-process theories (Yonelinas et al., 2010), this framework claimed that the hippocampus has the specific computational properties to give rise to recollection; whereas other MTL areas may be responsible for familiarity-based recognition (Norman & O'Reilly, 2003).

Due to the critical role of the hippocampus on episodic memory, its contributions to retrieval and its different expressions have received much attention (Aggleton, 2012; Merkow, Burke, & Kahana, 2015; Staresina, Fell, Do Lam, Axmacher, & Henson, 2012; Yonelinas et al., 2010; for a review see, Eichenbaum et al., 2007). However, neuropsychological studies have described a recollection and vividness impairment in patients with intact MTL but parietal or frontal damage (Davidson et al., 2008; Kopelman, Stanhope, & Kingsley, 1999; McDonald et al., 2006; Olson & Berryhill, 2009). Using functional magnetic resonance imaging (fMRI), it has extensively been delineated a hippocampal-neocortical network in which prefrontal (PFC) and posterior parietal cortex (PPC) work at the service of hippocampal retrieval mechanisms (Cabeza, Ciaramelli, Olson,

& Moscovitch, 2008; Rugg & Vilberg, 2013; Wagner, Shannon, Kahn, & Buckner, 2005).

The description of engagement of different brain regions during retrieval can be constructed using a temporal framework. Pre-retrieval functions involve the cognitive operations to process the cue or bias the search (Cabeza, Locantore, & Anderson, 2003; Rugg & Henson, 2003), as well as the top-down attention in order to maintain the retrieval goals (Cabeza, 2008). On the other hand, post-retrieval functions imply the evaluation and monitoring of the retrieval products close to the memory judgement (Achim & Lepage, 2005). In between, it takes place retrieval operations that may lead to successful recovery of information about the past experience (Rugg & Henson, 2003). In general, there is a certain consensus about the contributions of PFC to pre- and post-retrieval operations such as initiating and bias the retrieval towards high-order goals (Cabeza et al., 2003) or the top-down evaluation of the retrieved information to organise the following memory decision (Badre, 2008; Shimamura, 2011). In contrast, the functional role of PPC remains controversial, partially due to its functional segregation (Nelson et al., 2010). For example, the attention to memory hypothesis (Cabeza, 2008) extends the well-known role of parietal areas to direct and maintain attention to internally generated stimuli. From this perspective, the observed PPC activation is higher for associative memory because the amount of information to be attended increases the attentional demands (Ciaramelli, Grady, Levine, Ween, & Moscovitch, 2010). By contrast, another set of influential hypotheses proposes that the role of PPC is to represent retrieved content (Wagner et al., 2005) acting as an episodic buffer to maintain and integrate the information (Baddeley, 2000); consequently associative and item memory signals are directly related to the amount of information to be held (Vilberg & Rugg, 2008).

In conclusion, what is shared between all the models and theories here revisited is the idea that the fate of a memory trace depends on a dynamic interplay between several cognitive and brain mechanisms that well-orchestrated give rise to our complex experience of the world and ourselves. Addressing the challenging question of tracking how these mechanisms unfold demands: (i) taking into account the contribution of different brain regions (spatial resolution) and; (ii) examining every step of the mnemonic processing at the millisecond scale (temporal resolution)

4. Neural signals of episodic memory: from event-related responses to oscillations

4.1. Electrophysiological techniques

Much of the research on episodic memory has been conducted using fMRI the high spatial resolution of which has made it possible to explore the contribution of specific brain structures to the mnemonic processing. However, there are several advantages of electrophysiological techniques over fMRI that make them valuable tools to address cognitive processes. First, electrophysiological techniques can capture brain signals at the same time scale as cognition happens (milliseconds); therefore they offer an excellent and desirable *temporal resolution* to study how cognitive processes occur. Second, in contrast to haemodynamic techniques (BOLD signal), they provide a more direct measure of neuronal activity. The voltage changes and magnetic fields recorded on the scalp are meso- and macroscopic reflections of neuronal populations activity (Cohen, 2014; Lopes da Silva, 2013; Maestú, Ríos, & Cabestrero, 2008; Singh, 2012).

Moreover, although it may seem that MEG and EEG data comprises only two dimensions, time and space; we can actually extract information from at least four dimensions: time, space, power and frequency (Cohen, 2014). The present thesis takes advantage of the high dimensionality of MEG data under the assumption that the brain is a complex system that uses these dimensions to support our cognitive operations flexibly (Cohen, 2011). This high-dimensional data can be analysed in such way (e.g. oscillations) that the results are comparable with neurophysiological models and invasive recordings in humans and animals (Buzsáki, Anastassiou, & Koch, 2012; Buzsáki & Wang, 2012), therefore it arises as a pivotal method for cognitive neuroscientists.

4.2. Electrophysiological signatures of episodic memory

Historically, electrophysiological methods have been applied to measure time-locked deflections of the M/EEG signals, also known as *event-related potentials* or *fields* (ERP/ERFs). The inspection of the resulting waveforms after averaging several trials of a particular class (e.g. correctly recognised old vs new trials) set the foundations of our current knowledge about the temporal dynamics of memory processes.

A traditional question in memory research is what makes an event memorable, or in other words, what mechanisms need to be engaged during encoding to increase the probability of success during later retrieval. This question was first addressed using ERPs with the so-called *subsequent memory paradigm* comparing the neural activity during encoding for subsequently remembered vs. forgotten items (Paller, Kutas, Shimamura, & Squire, 1987). In general, subsequent memory effects – also known as difference due to memory– are identified as slow deflections 400ms after the stimulus onset (Paller, Kutas, & Mayes, 1987). Subsequent memory effects seem to be also sensitive to the levels of processing manipulation such that deep encoding elicits a frontal distribution of these components (Guo, Zhu, Ding, Fan, & Paller, 2004), whereas perceptual encoding does it over parietal sites (Paller et al., 1987). Based mainly on fMRI studies, there has been some controversy surrounding whether deep and shallow encoding engage different networks. Recent evidence points towards thinking that shallow encoding engages part of the deep encoding network, arguably because successful encoding either with deep or shallow processing shares a common hippocampal-prefrontal network (Baker, Sanders, Maccotta, & Buckner, 2001; Schott et al., 2013).

ERP/Fs have also proven their usefulness to accurately track the temporal dynamics of memory retrieval. Studies of recognition memory have thoroughly described '*old/new effects*' that arise when correctly recognised old and new stimuli are compared (for a review see Rugg & Curran, 2007). The dual-process theory (*see Retrieval*) has found strong support on ERP recognition memory results since two different neural signatures for familiarity and recollection emerge from the old/new paradigm. Numerous experiments have found early modulations (300-500ms) over mid-frontal electrodes linked to familiarity, whereas

recollection can be systematically tracked by a slower (500-700ms) left-parietal component (Rugg & Curran, 2007; Rugg & Yonelinas, 2003). Although ERP/F research has provided valuable insights about fundamental questions of episodic memory functioning, the physiological mechanisms underlying event-related responses are still poorly understood and make it difficult to unravel the functional significance of these robust findings.

As it was previously pointed out, M/EEG data contains more information –such as frequency– that is not exploited by ERP/Fs and enable to identify rhythmic fluctuations in the excitability of neuronal populations, i.e.: *brain oscillations* (Buzsáki & Watson, 2012), that can be interpreted in terms of neural mechanisms in a more straightforward manner than ERP/Fs (Cohen, 2014). This periodic synchronization of neuronal activity seems to be ubiquitous, and some of them are even visible in the unfiltered M/EEG signal to the bare eye, as is the case of the alpha rhythm (8-10 Hz). The relevance of brain oscillations in episodic memory lies in its role on coordinating different cell assemblies (Schnitzler & Gross, 2005) and creating precise time windows to regulate synaptic plasticity (Hanslmayr, Staresina, & Bowman, 2016).

In general, the description of brain oscillations is usually given considering frequency and amplitude changes, i.e. relative power increase or decrease at a certain frequency band (Hanslmayr & Staudigl, 2014). Perhaps the best known brain rhythm related to episodic memory in humans is the gamma rhythm (>30Hz). Evidenced by iEEG recordings in the human hippocampus (Burke et al., 2014; Long, Burke, & Kahana, 2014; Staresina et al., 2016) and over the scalp with MEG (Osipova et al., 2006), the gamma power increase seems to be linked to both successful encoding and retrieval. The interpretation of gamma power increases (synchronization) in terms of neurophysiological mechanisms comprises different views ranging from a direct increase of the neuronal firing rate (Miller et al., 2013) to the restriction of the firing rate to precise time windows via hippocampal interneurons inhibition (Axmacher, Elger, & Fell, 2008). Indeed, episodic memory in the hippocampus is not restricted to the gamma frequency, but it seems to be also regulated by other rhythms such as the theta oscillations. In cellular studies, for instance, a stimulus may or may not trigger *long-term potentiation* (LTP) in function of the moment in which it happens relative to the ongoing theta

oscillation (Pavlides, Greenstein, & Winson, 1988). Building on the compelling phenomenon of theta phase precession demonstrated in animal models (O'Keefe & Recce, 1993), it has been suggested that information may be encoded by timing instead of by the firing rate (for a review see Buzsáki, 2002). Theta phase precession termed the shift of the place cells' action potentials (spikes) to earlier phases with respect to the ongoing theta oscillation. Initially, the spikes arrive at late theta phases but when the rodent enters the cell's place fields, they occur at earlier phases (Colgin, 2013), and the inputs that arrive at the theta peak induce LTP (Axmacher, Mormann, Fernández, Elger, & Fell, 2006). Inspired by these animal results, recent recordings in the human hippocampus have also shown that the success of encoding may also depend on the precise firing relative to the phase of the theta oscillation (Rutishauser, Aflalo, Rosario, Pouratian, & Andersen, 2018) rather than on the firing rate.

Whereas gamma and theta rhythms are systematically found in the form of power increases on memory tasks (Nyhus & Curran, 2010), the lower frequencies (<20Hz), especially within the alpha band (8-12Hz), have displayed apparently contradictory behaviours. On the one hand, M/EEG studies using working memory paradigms have shown a strong alpha power increase linked to the memory load during the delay period (Jensen et al., 2002; Scheeringa et al., 2009). Whether alpha synchronization reflects engagement or disengagement of specific brain regions remains controversial. Early interpretations of alpha power increases posited that it was related to idling states (Pfurtscheller, 1992). However, more recent views suggest that alpha synchronization is related to the active processing of the representations during the maintenance period (Palva & Palva, 2007), and others claim that it reflects the inhibition of task-irrelevant areas (Jensen & Mazaheri, 2010; Klimesch, Sauseng, & Hanslmayr, 2007). On the other hand, both M/EEG and intracranial recordings using episodic memory tasks have demonstrated a robust alpha desynchronization during memory formation (Fellner, Bäuml, & Hanslmayr, 2013; Long et al., 2014) and retrieval (Hanslmayr, Staudigl, & Fellner, 2012; Michelmann, Bowman, & Hanslmayr, 2016; Staresina et al., 2016).

Using the abovementioned subsequent memory paradigm, later remembered items not only have been linked to an increase in theta and gamma band power (Düzel, Penny, & Burgess, 2010; Nyhus & Curran,

2010), but also to a decrease of the lower frequencies, i.e. alpha and beta band (Fellner et al., 2013; Hanslmayr et al., 2012; Klimesch, 1996; Weiss & Rappelsberger, 2000). Coinciding with fMRI studies (Paller & Wagner, 2002), these negative subsequent memory effects have been localised over inferior prefrontal regions (Hanslmayr et al., 2011; Meeuwissen, Takashima, Fernández, & Jensen, 2011) and, evidenced by intracranial iEEG, also in the hippocampus (Sederberg et al., 2007). As Hanslmayr et al., (2016) highlight, alpha desynchronization seems to emerge from the cortical regions specialised on processing the stimulus, inasmuch as subsequent memory effects of non-verbal material are localised over parietal and occipital areas (Noh, Herzmann, Curran, & De Sa, 2014). Similarly, alpha decreases during retrieval have emerged from those brain regions related to the sensory features of the retrieved content (Michelmann et al., 2016; Waldhauser, Braun, & Hanslmayr, 2016) and this decrease parametrically varies in function of the number of retrieved elements (Khader & Rösler, 2011).

Consistent with these findings and building on the complementary learning systems framework (*see Cognitive and neurobiological models of episodic memory*), Hanslmayr et al. (2016) have delineated an interesting proposal to unify these different synchronization and desynchronization results. To put it concisely, this framework considers that theta/gamma synchronization in the hippocampus and low frequencies desynchronization in the neocortex are reflecting the different but complementary labour of these two systems to support memory representations. It is postulated that neocortical desynchronization enables to represent the stimulus by engaging the specialised cortical modules; while hippocampal power increases enable one-shot learning and binding the context of the events (Staudigl & Hanslmayr, 2013) through gamma-to-theta synchronization similarly to the aforementioned theta precession phenomenon.

5. The knowledge gaps

Beyond the initial encoding, from the literature review emerges a recurrent but not fully understood phenomenon that seems to be one of the core mechanisms underlying the complexity of episodic memory: memory replay or reactivation. In general, the concept of reactivation has been linked to the study of memory consolidation during *offline* periods, either during sleep or wakefulness (Dudai, 2004; Dudai et al., 2015; Zhang, Fell, & Axmacher, 2018). However, recent views (Antony, Ferreira, Norman, & Wimber, 2017) also apply the concept of memory reactivation to *online* processing such when a cue triggers the retrieval of a previous experience. Interestingly, it has been proposed that online and offline reactivation may be supported by the same neural mechanisms and contribute similarly to episodic memory (Schreiner et al., 2018). However, while it seems to be a certain consensus on the impact of sleep reactivation on behaviour (Diekelmann & Born, 2010), little is known about the impact of awake reactivation. The available evidence came mainly from neuroimaging studies that capitalised on the reactivation of the spatial patterns to reveal its impact on consolidation and successful recall (Staresina et al., 2013; Tambini & Davachi, 2013). However, brain oscillations may play a key role in awake reactivation as happens during sleep, so further electrophysiological evidence is needed to understand whether oscillatory patterns may track reactivation as well.

The closer approach can be found in targeted memory reactivation procedures (Oyarzún, Morís, Luque, de Diego-Balaguer, & Fuentemilla, 2017; Schouten, Pereira, Tops, & Louzada, 2017) where there is a cue that triggers the memory replay. These cues may act as hallmarks to track the subsequent reactivation, however, when it comes to investigating spontaneous reactivation during wakefulness these hallmarks are lacking. Some key methodological advances might have opened the possibility of tracking episodic memory also during waking rest. Such is the case of a novel procedure based on frequency oscillatory entrainment (*see Chapter 4*) that has been successfully applied to tag memories during encoding and later observe its re-emergence from the EEG signal during the very first moments of retrieval (Wimber, Maaß, Staudigl, Richardson-Klavehn, & Hanslmayr, 2012). To date, this method has not been applied to post-encoding offline periods; therefore it still remains a need for an efficient

method to capture spontaneous uncued offline reactivation during wakefulness.

The possibility of reliably tracking offline memory reactivation will bridge the gap between encoding and retrieval to complete the puzzle of how our experiences become long-lasting memories. If the application of frequency-tagging during waking rest is successful, it will open the possibility to gain a deeper understanding of the nature of this reactivation: Is it like the reinstatement produced at retrieval or is it different? What are the brain mechanisms that underlie these processes and what is the functional role of neocortex and hippocampus?

By comparison, our current understanding of retrieval and consequently of online reactivation, is by far, much more comprehensive than for offline reactivation. Perhaps, recollection (*see Retrieval*) linked to the subjective feeling of re-experiencing a past event can be regarded as the complete memory reactivation phenomenon in humans. However, decades of thorough ERP/F and fMRI research on recollection remain apparently unconnected arguably because its neural mechanisms need clarification. With respect to the timing, it is well-established that M/EEG recollection effects unfolds few milliseconds after familiarity signals and can be tracked over left posterior sensors (Herron, 2007; Johansson & Mecklinger, 2003; Mecklinger, Rosburg, & Johansson, 2016; Rugg & Curran, 2007). In parallel and with higher spatial resolution, fMRI has systematically revealed a 'core recollection' network delineated around posterior parietal cortex and medial temporal lobe (MTL) regions (Hayama, Vilberg, & Rugg, 2012; Johnson, Suzuki, & Rugg, 2013; King, de Chastelaine, Elward, Wang, & Rugg, 2015; Rugg, Johnson, & Uncapher, 2015; Rugg & Vilberg, 2013; Thakral, Wang, & Rugg, 2017; Vilberg & Rugg, 2012). The temporal resolution of fMRI does not enable to directly explore what the underlying neural dynamics are and whether these regions are recruited for pre- or post-retrieval operations (*see Retrieval*). The basic knowledge of whether the temporal (ERP/F) and the spatial (fMRI) signatures of recollection are reflecting the same cognitive processing and neural mechanism is crucial to set the foundations of future questions regarding more subtle forms of online reactivation.

From the description of these issues can be appreciated the necessity of addressing the spatial and temporal dynamics of memory reactivation.

In contrast to fMRI, both MEG and EEG are electrophysiological techniques that provide a direct and time-resolved measure of brain activity. Unlike electric currents, magnetic fields do not suffer distortions through the brain and head tissues, yielding a more precise source mapping (Baillet, 2017; Maestú et al., 2008). Therefore, MEG arises as an excellent tool to fill the aforementioned gaps: tracking offline and online reactivation through time and space to get a deeper understanding of consolidation and retrieval processes.

Chapter 3

Purpose statement

1. General purpose

The essential questions and experimental studies of this thesis are grounded in the integration of the frameworks and evidence outlined in the previous chapter. The general purpose is to yield an account of how oscillatory activity tracks cognitive operations and memory reactivation during consolidation (offline) and retrieval (online).

2. Research questions: objectives and hypotheses

This thesis aims to fill two critical gaps in our understanding of determinant aspects of different expressions of memory reactivation:

2.1. Consolidation: Can consolidation be tracked by the reactivation of specific oscillatory patterns during waking rest?

Modelled on the preceding successful application of oscillatory entrainment to episodic memory retrieval (Wimber et al., 2012), the first study (*Chapter 4*) will combine the use of frequency-tagging with different levels of processing (Craik & Lockhart, 1972) during encoding. These experimental manipulations aim to explore the re-emergence of the entrained frequencies during awake post-encoding offline periods. The use of MEG intends to take advantage of its spatiotemporal resolution to

answer to what extent the reactivation of oscillatory patterns emerges from the currently proposed consolidation circuits. If oscillatory reactivation is successful, the final goal is to unveil the physiological meaning of reactivation, establishing a link with subsequent memory performance.

Memory reactivation during post-encoding waking rest should be reflected on the MEG signal as a specific power increase of the entrained frequencies (Cohen, 2014). Then, if reactivation is linked to successful memory performance (Staresina et al., 2013), as long as deep encoding produces better memory, it would also lead to higher reactivation rates than after shallow encoding. Lastly, source space analysis may reveal that memory reactivation emerges from medio-temporal and prefrontal regions (Frankland & Bontempi, 2005; Preston & Eichenbaum, 2013). Finally, if reactivation has an impact on behaviour, the participants that display higher reactivation rates should also show better memory performance. These results may have implications in our current models of systems consolidation. Besides, they might open the possibility to unveil how unconscious and spontaneous memory reactivation is coordinated in the human brain.

2.2. Retrieval: Can alpha rhythms unite ERP/ERFs and BOLD-fMRI recollection signatures to simultaneously track its temporal and spatial dynamics?

In the second study (*see Chapter 5*), an associative memory recognition test was used to study the neural mechanisms underlying recollection. Based on the previous literature that links alpha rhythms to ERP (Mazaheri & Jensen, 2008) and BOLD-fMRI (Laufs et al., 2006), alpha oscillations arise as the best candidate to track simultaneously the temporal and spatial dynamics of recollection. A trade-off between temporal and spatial resolution is achieved by analysing MEG signals at the sensor and source space (Baillet, 2017).

First, based on ERP/Fs research, it is expected that recollection signals start after the familiarity effect over posterior sites in the sensor space. Second, source space analysis should reveal that this effect emerges from the regions pinpointed by fMRI studies: mainly, posterior parietal cortex

and hippocampus. Finally, these findings may be linked to the existent electrophysiological evidence (M/EEG and intracranial recordings) such that some of the existing theories of recollection will be made more robust.

3. Significance of the thesis

Memory is at the core of human cognition. We are particularly aware of its centrality when it comes to facing memory impairment or recurrent traumatic memories. This thesis, however, will not provide a direct answer to these dramatic problems. As it usually happens in basic science, the contribution of this thesis is providing empirical evidence to expand our knowledge about memory reactivation. This evidence is integrated into theories and models that may serve as driving force for future clinical and technological advances. That said, it is to be expected that the methodology and implications of the present work impact on our current understanding of episodic memory. Notably, because this would be the first time that spontaneous reactivation during wakefulness is captured by means of oscillatory patterns. Furthermore, our data may strengthen those models that highlight the role of mPFC-MTL circuit on consolidation. Secondly, although recollection is a well-known retrieval phenomenon, the oscillatory mechanisms that coordinate such a vivid memory reactivation are still unclear. The possibility of tracking recollection through its temporal and spatial oscillatory signatures may provide a shared ground to unify the literature. Overall, these data may be integrated in psychological theories about retrieval and consolidation, as well as neurocognitive models on how brain oscillations support cognitive operations. In the short term, our novel oscillatory entrainment procedure will provide a new methodological tool for neuroscientists to disentangle cognitive processes without an observable behavioural correlate (i.e.: speech processing, emotion…). In the long term, our findings may enable to track the cognitive and neural hallmarks of some medical conditions (i.e.: Alzheimer's disease or autism), successful learning strategies, as well as developing treatments to alleviate the recurrence of traumatic memories.

Chapter 4

Experimental study I: Consolidation

Oscillatory entrainment tracks spontaneous episodic memory reactivation during waking rest

Highlights

- Frequency-tagging and depth of processing enable tracking spontaneous offline reactivation.
- Offline reactivation over frontal sensors followed deep encoding, but not shallow encoding.
- Reactivation emerged from mPFC, inferior frontal gyrus and MTL regions.
- Prefrontal-hippocampal oscillatory reactivation predicts later recollection.

1. Introduction

How do our ephemeral experiences become long-lasting memories? After the formation of the memory trace, consolidation processes transform the recently acquired experiences into more stable and durable memory traces (Dudai, 2004; Frankland & Bontempi, 2005). One hypothesised mechanism to support consolidation is *memory replay* defined as the reactivation of the brain activity specific to the previous experience during post-encoding offline periods (Buzsáki, 1989; Gardner & Moser, 2017; Káli & Dayan, 2004; Marr, 1971). While sleep studies systematically find memory stabilisation and enhancement (for a review, see Diekelmann & Born, 2010), this may not be the only period during which consolidation takes place. Indeed, studies in rodents found awake reactivation of those firing patterns displayed during the previous experience (Carr et al., 2011; Gardner & Moser, 2017). Therefore, it

seems that post-learning offline reactivation is not restricted to sleep periods. In humans, for instance, task-specific hippocampal-cortical connectivity patterns can be observed again during waking rest periods (Tambini, Ketz, & Davachi, 2010). Moreover, fMRI representational similarity analysis provided compelling evidence that the amount of spontaneous reactivation of specific paired-associate items in the entorhinal cortex predicts subsequent associative memory performance (Staresina et al., 2013). Beyond the MTL, the medial prefrontal cortex (mPFC) seems to be a critical structure to boost consolidation. Applying a paired-associate memory task with rodents Tse et al., (2011) have revealed the causal role of the mPFC, particularly when it comes to consolidating information that can be integrated into previous schematic knowledge. Critically, the pharmacological blockade of this region after encoding suppressed the retrieval of recent and remote information.

In parallel, a recent set of EEG experiments with a cue-triggered paradigm has shed light on the neural mechanisms involved in memory reactivation during NREM sleep (Cairney, Guttesen, El Marj, & Staresina, 2018) and wakefulness (Schreiner et al., 2018). Remarkably, the MEG study of Schreiner et al. (2018) demonstrated that reactivation during both physiological states is supported by theta oscillations in medio-temporal and left-frontal regions. Although they found an interesting autonomous reactivation with a frequency of 1Hz while participants slept, this fluctuating reactivation was also triggered by a cue, so evidence for spontaneous memory reactivation is still lacking.

The main obstacle to study spontaneous offline reactivation during waking rest is the difficulty to pinpoint a trigger or a time window in which reactivation may happen. Our current understanding of the sleep architecture allows to detect natural triggers such as spindles (Antony et al., 2018) or hippocampal ripples (Zhang et al., 2018). However, during waking rest, there is no landmark to track reactivation and any externally-presented cue might mix up consolidation with retrieval mechanisms. A possible solution to this issue may be the use of the flicker effect to tag memories and track them in the M/EEG signals. The flicker effect –also known as frequency-tagging, steady-state responses (SSRs) or steady-state visual evoked potentials (SSVEPs)– is hypothesised to be generated by the entrainment of a brain oscillation to a rhythmic stimulation (Herrmann, 2001). Electrophysiological experiments demonstrated that a light that

flickers at a particular frequency, e.g. 10Hz, drives a synchronization in the visual cortex at the same frequency in such a way that a response at 10Hz can be recorded in the human M/EEG (Regan, 2009). This frequency-specificity arises as a powerful tool to track cognitive processes since different stimulus can be associated to different frequencies. In practice, the entrainment produces specific power changes in the M/EEG signal that can be isolated after the spectral decomposition (Cohen, 2014). This effect is not limited to the visual cortex and has also been found in broader networks (Ding, Sperling, & Srinivasan, 2006). Despite the lack of consensus surrounding whether the flicker effect is generated by the entrainment of an oscillation (Thut, Schyns, & Gross, 2011) or by the superposition of a series of ERPs (Capilla, Pazo-Alvarez, Darriba, Campo, & Gross, 2011), this question should only affect the neurophysiological interpretation of the flicker effect, not its usefulness to track cognitive processes (Cohen, 2014). Indeed, this method has successfully been applied to tag memories in an EEG experiment (Wimber et al., 2012) that demonstrated the emergence of the tagged frequencies during a likely unconscious memory reactivation at early stages of retrieval. Thus, frequency-tagging seems to be a good candidate for bypassing the lack of endogenous triggers during waking rest. The rationale behind this approach is that each frequency-tag may act as a distinctive feature of the event that enables to compare later whether the emergence of the oscillatory pattern is due to the resting ongoing oscillatory activity or the actual memory reactivation.

One of the most robust behavioural manipulations in episodic memory research is based on the levels of processing during encoding tasks (Craik & Lockhart, 1972) (*see Encoding*). In brief, it has been widely replicated that attending to the meaning of the stimuli (‘*deep processing*’) yields a significant boost in later retrieval in comparison to focusing on the non-semantic features of the stimuli (‘*shallow processing*’) (Galli, 2014). These encoding tasks lead to the engagement of partially different brain networks, with deep processing more reliant on the hippocampus than shallow processing (Otten, Henson, & Rugg, 2001; Schott et al., 2013). Since episodic memory reactivation seems to be coordinated by hippocampal-neocortical interactions (Rasch & Born, 2013), different levels of processing during encoding may lead to different rates of reactivation during waking rest.

In general, low frequencies generate stronger entrainment effects (Herrmann, 2001), and previous accounts of topographical changes related to cognitive processes have been mainly found within the alpha band (Silberstein, Danieli, & Nunez, 2003; Vialatte, Maurice, Dauwels, & Cichocki, 2010). Hence, to assess whether frequency tagging can be used to track spontaneous (uncued) reactivation during post-learning offline periods, we used two flickering backgrounds in the alpha range (8.6 and 12 Hz) associated to different encoding tasks during a paired-word associative memory task. This is the first time that oscillatory entrainment is used to study memory consolidation and based on the previous literature three main hypotheses might be contrasted: (i) frequencies associated to the deep encoding task might lead to higher rates of reactivation during post-learning periods, quantified by frequency-specific power changes in the MEG signal; (ii) reactivation might correlate with better associative memory recognition; (iii) reactivation might emerge from medio-temporal and prefrontal regions.

2. Materials and Methods

2.1. Participants

15 healthy right-handed subjects (9 females; mean age: 24 years, range: 18-37) with normal/corrected to normal vision. Participants gave written informed consent before participating. The study was approved by the University of Cambridge Psychology Research Ethics Committee.

2.2. Behavioural analysis

We wrote our experiment in MATLAB using the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997). Behavioural data were processed and analysed using a custom-written code for MATLAB.

2.3. Experimental procedure

The experiment was conducted inside the MEG shielded room with the participant seated upright. A schematic diagram of the experimental paradigm can be found in *Figure 5*.

Participants completed eight encoding-retrieval runs with 60 seconds of resting before and after each encoding phase in which they were asked to look at a central fixation cross. Throughout the present study, the terms *pre- and post-encoding offline periods* will be used to refer to this resting phase.

During encoding, participants were presented with pairs of English nouns. We used two different encoding tasks that varied in the depth of processing: a *syllable task* in which participants indicated how many of the two words contained 2 syllables (0, 1 or 2; *shallow encoding*), and an *imagery task* in which participants vividly imagined the two objects interact and indicated their imagery success (low, medium, high; *deep encoding*). Each word pair remained on the screen for 4 seconds regardless of the participant's response. Incidental to the encoding task, a flickering background, flickering at 8.6 or 12 Hz, was presented on the left or right side of the screen which participants were instructed not to pay attention. The visual-hemifield manipulation during encoding is beyond the scope of the current study, but counterbalancing ensured that deep and shallow encoding trials were equally often presented with both flicker rates and at both visual hemifields. Each encoding block contained 28-word pairs, with deep and shallow tasks alternating every 7 trials. In general, the flicker effect takes several milliseconds to stabilise (Cohen, 2014), therefore during the transition time (4 seconds) between blocks, the flicker was presented 2 seconds before the first trial of the block appeared.

During the retrieval phase of each run, 14 new words were mixed with a randomly chosen word of each of the 28 old word pairs. The display of a fixation cross preceded each trial during a jittered intertrial interval of 850 to 1150ms. The retrieval task was conducted in two steps; first, participants were asked to indicate whether the word was: (i) old and they also remember the paired associate, (ii) old, but they did not have any recollection of the paired associated, or (iii) new. The word remained on the screen during 4 seconds irrespective of the participant's response, which was collected with a single button press.

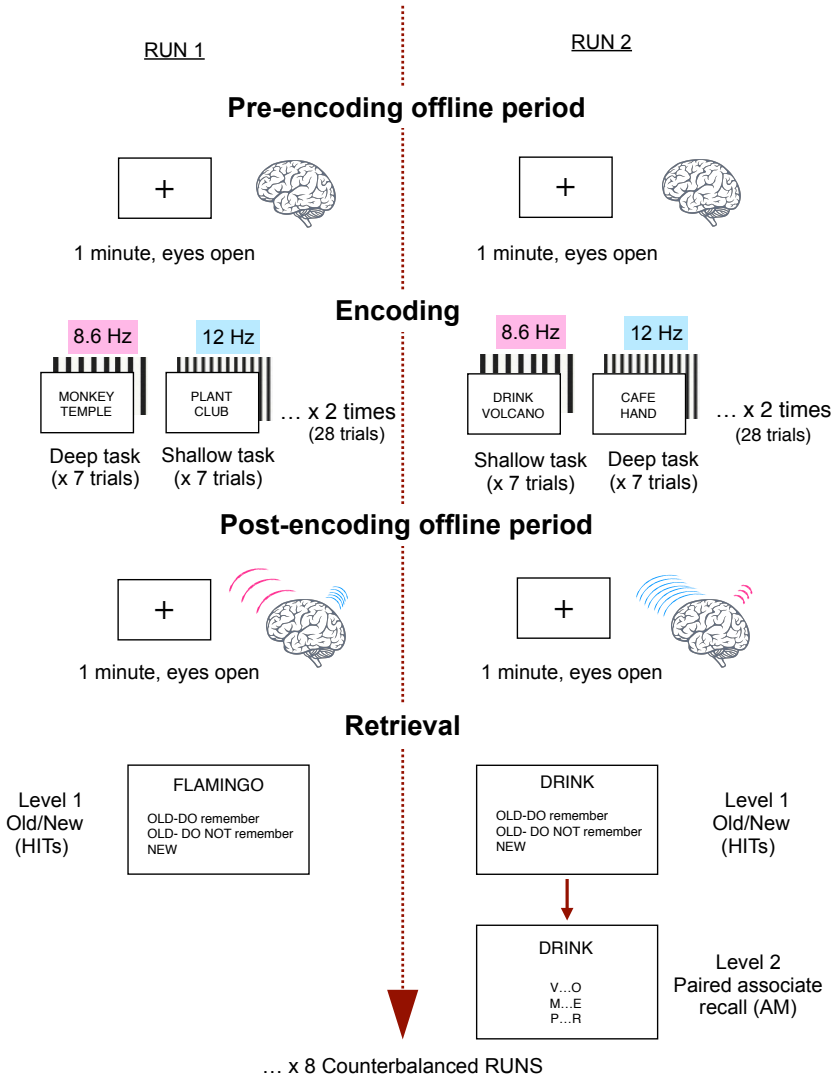

Figure 5. Study I Experimental procedure. During encoding, participants were asked to perform deep (imagery task) and shallow (syllable counting) processing of pairs of words. Simultaneously, a flickering background was presented at either 8.6 or 12 Hz, counterbalancing all conditions across runs. Each study phase was preceded and followed by an offline period of 1 minute during which participants were asked to look at a fixation cross. Post-encoding reactivation hypothesis is illustrated by the big and small echoes emerging from the brain depiction. We expected to see greater reactivation for deep encoding vs shallow regardless the frequency-tagging. During retrieval, participants saw a mixture of old and new words ('lures') and had to indicate with one button press whether they thought the given word was new, the word was old but they did not remember the paired associate or the word was old and they recalled the paired associate (as illustrated in RUN 1). In the latter case (as illustrated in RUN 2), a second validation screen appeared to validate recall accuracy, providing three first-last letter combinations of which one corresponded to the target association.

As illustrated in *Figure 5*, when participants selected the first option, a validation screen appeared during 2 seconds with three first-and-last letter combinations, one of which corresponded to the paired associate. Note that this two-step retrieval task maintained the stimulus display and response options constant for the first 4 seconds while providing an objective measure of recollection. With the aim of linking offline reactivation to subsequent memory performance, the following two conditions of interest were defined: HITs (trials in which participants indicated they recognized the word independently of their recollection of the paired associate) and Associative Memory (AM, trials in which participants indicated they recognized the word and remembered the paired associate, followed by a correct response during verification).

2.4. MEG Recordings

Data were recorded in a magnetically shielded room at the MRC Cognition and Brain Sciences Unit de la Universidad de Cambridge (UK, *http://www.mrc-cbu.cam.ac.uk*)[3] using a 306-channel VectorView MEG system (Elekta Neuromag, Helsinki). Data were sampled at 1 kHz with a highpass filter of 0.03 Hz. Only 204 planar gradiometers were used in the analysis. Head position inside the MEG helmet was continuously monitored using five head position indicator coils (HPI). A 3D digitizer (Fastrack Polhemus Inc., Colchester, VA, USA) was used to record the location of the HPI coils and the general head shape relative to three anatomical fiducials (nasion, left and right preauricular points). To track eye movements and blinks, bipolar electrodes were attached to obtain horizontal and vertical electrooculograms (HEOG and VEOG).

2.5. MEG preprocessing

MEG data were cleaned of external noise using the Maxfilter 2.0 software (Elekta Neuromag), applying the Signal-Space Separation (SSS) method with movement compensation (Taulu & Simola, 2006),

[3] These data belong to a project supervised by Dr. Berhard Staresina (University of Birmingham, UK) and with collaboration of Dr. Richard Henson (University of Cambridge, UK) and Dr. Maria Wimber (University of Birmingham, UK). Data collection was managed by Dr.Maria Wimber and Dr.Bernhard Staresina at the MRC Cognition and Brain Science Unit, University of Cambridge (UK). Further authorised developments for the present doctoral thesis were undertaken at the University of Birmingham and the Complutense University of Madrid as part of this PhD project.

correlation limit of 0.9 and time window of 10 seconds. Next, data were preprocessed and subsequently analysed with the FieldTrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011) running in MATLAB. For encoding analyses, data were segmented into trial epochs from -2 to 4s time locked to stimulus onset. For the offline periods (pre- and post-encoding), data from the 60s of each offline period were segmented into epochs of 5s. In both cases, clean data were then downsampled to 200 Hz.

After discarding trials with muscle and jump artifacts by trialwise inspection, an Independent Component Analysis was computed. Independent components reflecting eye movements and heartbeat were identified by visual inspection of component scalp topographies, time courses and its comparison with EOG/ECG raw time-series. Noise components were removed, and clean trials were visually inspected again in order to identify and remove any remaining artefact (*Table 1*)

Conditions	Average	Range
Encoding		
8.6 Hz flicker	100	65 – 112
12 Hz flicker	100	83 – 111
Deep task	100	71 – 111
Shallow task	100	77 – 111
Pre-encoding offline period		
Deep 8.6 Hz & Shallow 12 Hz	43	24 – 48
Deep 12 Hz & Shallow 8.6 Hz	44	25 – 48
Post-encoding offline period		
Deep 8.6 Hz & Shallow 12 Hz	43	24 – 48
Deep 12 Hz & Shallow 8.6 Hz	44	33 – 48

Table 1. Number of trials after artifact-rejection for encoding and offline periods

2.6. Quantification and statistical analysis

2.6.1. Power analysis

Power spectra were obtained for each artifact-free encoding trial using the Fast Fourier Transform (FFT) with a Hanning taper, as implemented

in Fieldtrip. To increase the frequency resolution (Cohen, 2014) in order to capture 8.6 and 12Hz frequencies, 10 seconds of zero padding were added to the actual trial. Frequencies of interest were defined in 0.1Hz steps from 5 to 15Hz, and this procedure was applied to the sensor and the source-space data. For the sensor-space analysis, the power values were obtained for the vertical and horizontal component of the estimated planar gradient and then combined.

2.6.2. Topography of power oscillatory entrainment during encoding

To capture the maximal effect of the flicker entrainment for each subject, we defined a frequency-window of 1Hz centred on the actual flicker frequency, that is, between 8.1-9.1Hz for the 8.6Hz condition and 11.5-12.5Hz for the 12Hz condition. For the subsequent analyses, the power in each frequency-window of interest was averaged for each subject and flicker condition, yielding two power values (8.1-9.1Hz and 11.5-12.5Hz) for the two flicker conditions (8.6 and 12Hz) per subject.

To quantify the oscillatory entrainment during encoding, the power increase due to the flicker stimulation was calculated as the power when a specific frequency was entrained (stim) relative to the power when it was not (sham) (*Figure 7A*). For example, the 8.6Hz entrainment effect was estimated as the power increase between 8.1-9.1Hz of the trials in which the screen flickered at 8.6Hz relative to the 8.1-9.1Hz power of the trials in which it did not, namely, when the screen flickered at 12Hz. This procedure was undertaken regardless of the encoding task tagged by the flicker, such that it enabled to control for the overall power increase that a flickering screen may produce at unspecific frequencies.

The schematic diagram displayed in *Figure 7A* can also be summarised as follows:

$$8.6\ Hz\ Oscillatory\ entrainment = \frac{(8.1-9.1\text{Hz})\text{mean power of trials with 8.6 Hz stimulation (STIM)}}{(8.1-9.1\text{Hz})\text{mean power of trials with 12 Hz stimulation (SHAM)}}$$

$$12\ Hz\ Oscillatory\ entrainment = \frac{(11.5-12.5\text{Hz})\text{ mean power of trials with 12Hz stimulation (STIM)}}{(11.5-12.5\text{ Hz})\text{ mean power of trials with 8.6 Hz stimulation (SHAM)}}$$

This procedure resulted in a topographical map of the oscillatory entrainment in each flicker condition (*Figure 7B*), Next, these maps were averaged across flicker conditions. The possible scenario in which the flicker would not produce oscillatory entrainment might yield a result of 1, therefore, to statistically test whether the flicker entrainment produced an effect, a dependent-samples T-Test against no relative power increase (flicker effect = 1) was performed (*Figure 7C*). Again, to correct for multiple comparisons across channels, we used a non-parametric cluster-based permutation test (Maris & Oostenveld, 2007), setting the cluster alpha at .025.

2.6.3. Encoding conditions specificity: Multivariate pattern analysis (MVPA)

To test the specificity of the frequency-tags during the encoding phase, we asked whether the cognitive (deep vs shallow) and the perceptual (flicker 8.6 vs 12 Hz) representations could be decoded from the power spectrum. With this aim, power spectra from 1 to 30 Hz were obtained for each artifact-free encoding trial using the Fast Fourier Transform (FFT) with a Hanning taper, as implemented in Fieldtrip. Power spectra were obtained for each artifact-free encoding trial using the Fast Fourier Transform (FFT) with a Hanning taper, as implemented in Fieldtrip. Frequencies of interest were defined in 1Hz. Next, a Linear Discriminant Analysis (LDA) as implemented in CosmoMVPA MATLAB toolbox (Oosterhof, Connolly, & Haxby, 2016) was used to classify: (i) deep vs shallow; and (ii) 8.6 vs 12 Hz flicker; using frequencies as features for each sensor.

To test the ability of the classifier to generalised the trained discrimination to new data (Grootswagers, Wardle, & Carlson, 2017) we used a *k*-fold cross-validation procedure. Following this procedure the accuracy estimate of the classification is the average of the accuracies derived in all the *k* iterations. Since in M/EEG data, each trial is independent of the rest (Oosterhof et al., 2016), several combinations of training and testing sets can be constructed. In this case, we conducted a 5-fold procedure in which a subset of 20% of the trials in each iteration was used to test the performance of the classifier. For example, if a participant had a number of 244 trials in the encoding phase, 180 trials

were used to train the classifier and 44 to test its performance. In this way, we controlled for overfitting since a trial used for training was never used for testing. We repeated this procedure for each sensor and participant in each of the two comparisons of interest. This procedure resulted in two decoding maps (accuracy): cognitive and perceptual per participant.

To statistically assess whether the averaged accuracy was different from chance (null-effect), we performed a dependent-samples T-Test against chance level (0.5) for each decoding map (*Figure 8A and B*). To correct for multiple comparisons across sensors, we used a non-parametric cluster-based permutation test (Maris & Oostenveld, 2007), setting the cluster alpha at .025 (one-tailed). Since this procedure was undertaken separately for the cognitive and the perceptual maps (yielding two more comparisons), the level of significance was corrected using the Bonferroni method ($p = .0125$).

Finally, to test the specificity of the cognitive and perceptual representations, we did a two-tailed dependent T-Test comparing these two maps. Again, to correct for multiple comparisons across sensors, we used a non-parametric cluster-based permutation test (Maris & Oostenveld, 2007), setting the cluster alpha at .025 (*Figure 8C*).

2.6.4. Evidence for sensor-space offline reactivation

As illustrated in *Figure 6*, assessing offline reactivation was done in two steps. First, on a run-by-run basis and for each pre and post-encoding offline period separately, two reactivation indexes were derived as a function of the frequency-tag. Next, these two reactivation indexes were collapsed across runs as a function of the encoding task (deep or shallow). For example, one possibility was that the offline period of interest preceded or followed an encoding block in which 8.6Hz tagged deep processing and, in turn, 12Hz tagged shallow processing. In this case, the mean power from the frequency range centred on 8.6Hz (8.1-9.1Hz) was used as an index of deep offline reactivation whereas the mean power from the frequency range centred on 12Hz (11.5-12.5Hz) was used as an index of shallow offline reactivation, for this specific run. Note that from each run a measure of the power for deep and shallow reactivation is derived although not in every run it came from the same frequency. Then,

in a second step, deep and shallow measures were collapsed across runs, such that subsequent analysis was focused on the offline reactivation regardless of the specific frequency-tagging. The final output of this procedure was the mean power for each encoding task (deep and shallow) in each phase of the experimental paradigm (pre- and post-encoding) per each sensor (102) and subject (15).

The statistical analysis was done for the deep and shallow reactivation indexes separately. To statistically test if reactivation indexes can differentiate pre and post-encoding, a dependent-samples T-Test was performed. To correct for multiple comparisons across channels, we used a non-parametric cluster-based permutation test (Maris & Oostenveld, 2007), setting the cluster alpha at .025. However, since this procedure was undertaken separately for deep and shallow encoding (yielding two more comparisons), the level of significance was corrected using the Bonferroni method (p = .0125).

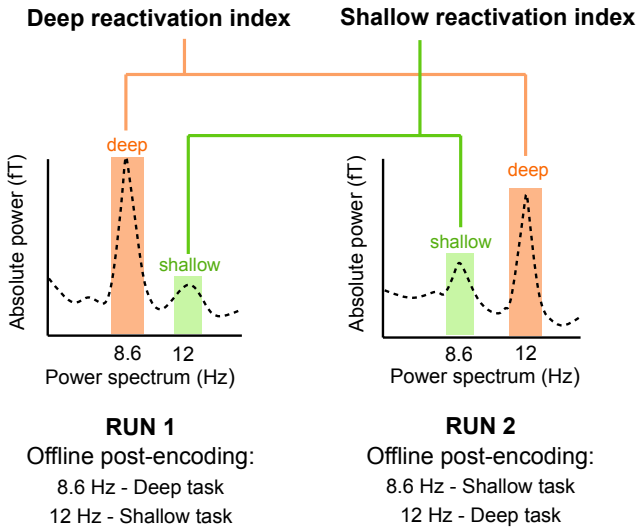

Figure 6. Schematic diagram of the procedure to compute deep and shallow reactivation indexes for offline periods. Offline analysis was done for each run separately (the illustration depicts only two runs with the two possible combinations). From each pre- and post-encoding offline period two reactivation measures were derived by averaging the power of each flicker frequency range (8.6 and 12 Hz). Afterwards, as a function of the encoding task (deep or shallow), these measures were collapsed across runs, yielding a separate reactivation index for deep and shallow encoding. Note that deep power increase is proposed to be higher than shallow based on our hypothesis.

2.6.5. Control analysis: specificity of the offline reactivation

A potential broadband power increase during post-encoding offline periods led by the preceding flicker stimulation relative to the pre-encoding offline period, might be a confounding factor. Thus, to test whether the observed effects emerged from the specific flicker frequency reactivation and not by a generalised power increase, the same reactivation indexes were obtained for the frequencies centred on 10.3Hz (9.8-10.8Hz). Notice that, to ensure a fair comparison, this frequency range is equidistant from both experimental flicker frequencies (8.6 and 12 Hz).

2.6.6. Source reconstruction

To estimate the underlying brain activity for the reactivation (8.6 and 12Hz) power effects found at the sensor level, we performed the source reconstruction of the power from 5 to 15Hz. First, a regular grid of 1825 points with 10 mm spacing was created in the Colin27 MRI template (Collins et al., 1998) using Fieldtrip's brain segmentation tools. Then, this set of points was transformed into each participant's space using the individual headshapes derived from the 3D head digitalization. The forward model was solved with a single-shell method, and the source reconstruction was performed using the linearly constrained minimum variance (lcmv) beamforming approach implemented in Fieldtrip. A common filter was constructed to ensure reliable comparison between conditions: the spatial filter's coefficients were obtained from the average covariance matrix from all pre and post-encoding offline trials and then this filter was multiplied to each condition separately. In all the cases, filters were derived for artifact-free data from 5 to 15 Hz. The final output consisted of a time series estimate per source location, condition (pre and post-encoding) and subject. Finally, the power spectrum was obtained with the same settings and procedure as in the sensor-space data (*see Power analysis*).

2.6.7. Evidence for source-space offline reactivation

Significant effects in the sensor-space were later mapped onto the source space following the same procedures that were previously used to

obtain the power spectrum and the reactivation indexes in the sensor-space. To statistically test the source-space reactivation effects (post vs pre-encoding offline power), we conducted a dependent-samples T-Test. We again used a non-parametric cluster based permutation test with an alpha of .025 to correct for multiple comparisons across source locations.

2.6.8. Relationship between reactivation and behavioural performance

To investigate the physiological meaning of the reactivation, the power at the source locations within the significant clusters was separately averaged for pre- and post-encoding offline periods. Post-encoding power increase of each participant was calculated by subtracting the corresponding pre-encoding offline period power. These reactivation values where then correlated with participants' performance on the associative memory task (recall of the paired associate /HITs). To this end, Pearson correlation was used with an alpha of .05 (two-tailed) (*Figure 11*)

3. Results

3.1. Behavioural results

In order to track the reactivation during offline-periods we used a well-known behavioural manipulation of episodic memory: the levels of processing, associated with a flickering background to entrain brain oscillations at 8.6Hz and 12 Hz.

3.2. Encoding reaction times (RTs)

For RTs, a two-way repeated measures ANOVA with the factors Task (deep, shallow) and Flicker frequency (8.6, 12 Hz) revealed a main effect of the Task ($F_{(2,14)} = 22.66$; $p<.01$). There was no significant interaction Task x Flicker frequency ($p=.61$) nor main Flicker frequency effect ($p=.29$). For the main effect of the encoding task, the post-hoc dependent-samples T-Test revealed that reaction times were significantly longer for

deep (mean = 2.47, SEM = .09) than for shallow encoding (mean = 2.02, SEM = .08) ($t_{(14)}$ =4.76, p<.01).

3.3. Subsequent memory performance

Since all the statistical analyses were conducted collapsing across flicker frequencies, subsequent memory performance was focused on the task manipulation (deep vs shallow). As illustrated in Figure 5, retrieval was tested on two levels. The first level comprised an old/new decision quantified by the HITs rate: the proportion of correctly recognised old items out of the total amount of previously studied items. The second level comprises the paired associate recall that was operationalised as the proportion of correct paired associate responses out of the number of HITs.

As the levels of processing framework predicts (Craik & Lockhart, 1972), overall retrieval was better (*Table 1*) for deep than for shallow processing (collapsing across flicker frequency conditions), indicated by the better subsequent memory performance for both levels: HITs ($t_{(14)}$ =5.80, p<.01) and Pair associate recall ($t_{(14)}$ =7.77, p<.01).

	Subsequent memory performance			
	HITs rate		Pair associate recall	
Encoding task	Mean	SEM	Mean	SEM
Deep processing	0.88	0.02	0.55	0.06
Shallow processing	0.56	0.08	0.14	0.04

Table 2. Subsequent memory performance for HITs and associative memory. The HITs rate denotes the amount of correctly recognised old trials out of the total of previously studied items. The proportion of Pair associate recall denotes the amount of correctly recollected paired associates out of the HITs

3.4. Topography of the power entrainment during encoding

Following the procedure described in *Figure 7A*, we quantified the power entrainment during encoding as the relative power increase when a frequency was entrained over when it was not. As expected, when we compared the collapsed power entrainment maps (*Figure 7C*) against a

possible null effect (stim/sham = 1) a positive cluster (p <.01) emerged from posterior sites of the helmet. Therefore, the posterior sensors seemed to be the most sensitive to the flicker manipulation.

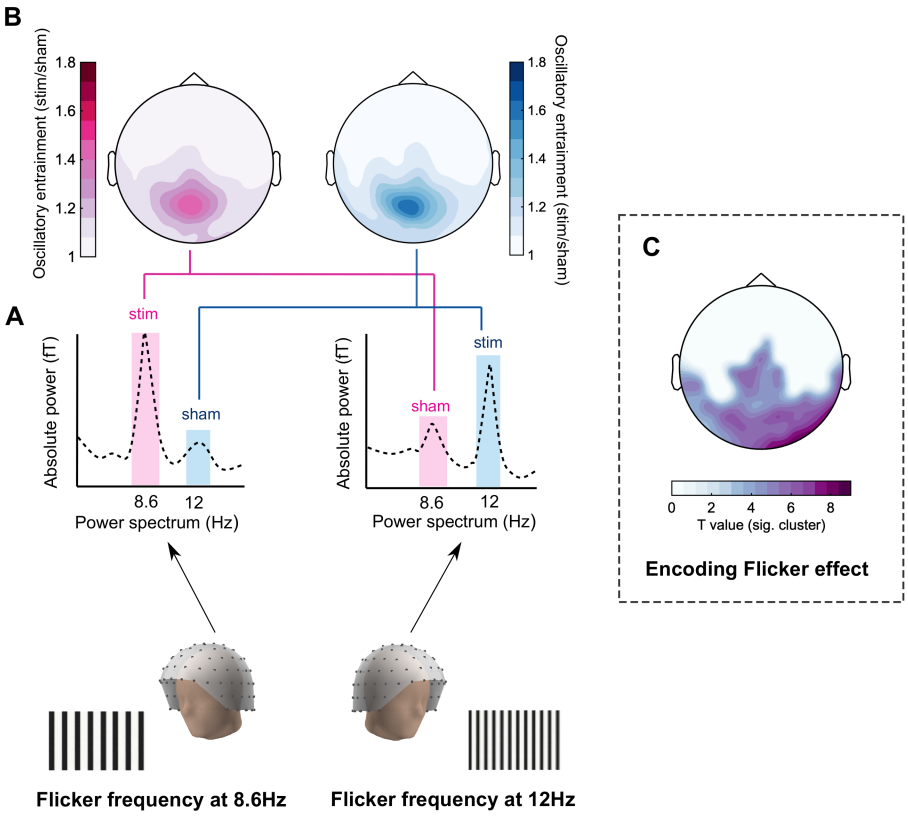

Figure 7. Topography of the flicker effect. (A) Analysis approach to address the topography specificity of the flicker effect. (B) Oscillatory entrainment topography in each frequency-tag showing a relative increase over posterior sensors (C) T-test result for the comparison of the oscillatory entrainment relative increase (stim/sham) against a potential null effect (stim = sham). The significant cluster (p<.01) shows a robust entrainment pattern over posterior zones of the helmet.

3.5. Cognitive and perceptual representations can be decoded from the power spectrum during the encoding phase

As shown in *Figure 8A and B*, cognitive (deep vs shallow) and perceptual (flicker 8.6 and 12 Hz) representations can be decoded at the level of single trial from the power spectrum. This result suggests that class-specific information about the encoding conditions is contained on

the power patterns. We noted that the sensors with higher significant decoding accuracies were found over frontal sites for the cognitive discrimination (*Figure 8A*) and over posterior sites for the perceptual discrimination (*Figure 8B*). This means that the power patterns of the frontal sensors enabled to discriminate deep vs shallow at the level of single trial; whereas posterior sensors do so for 8.6 and 12Hz flicker. It follows from this result that encoding conditions where highly specific.

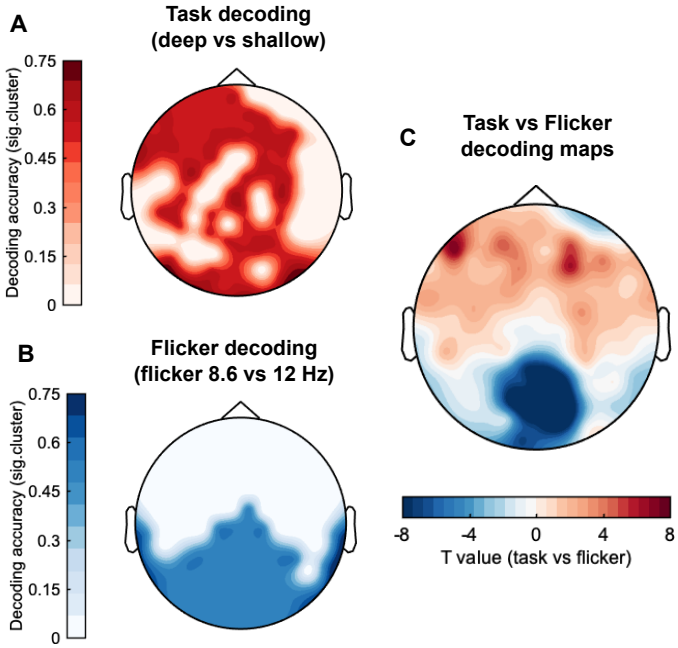

Figure 8. Decoding of cognitive and perceptual representations. (A) Decoding of the cognitive representation (deep vs shallow). Topoplot values represent the accuracy of the significant cluster (p<.01) from the T-test for the comparison against chance level (B) Decoding of the perceptual representation (flicker 8.6 vs 12Hz). Topoplot values represent the accuracy of the significant cluster (p<.01) from the T-test for the comparison against chance level (C) T-test result for the comparison of the task and flicker decoding maps. The significant positive and negative clusters shows a robust difference between cognitive and perceptual representations.

When comparing cognitive (task) and perceptual (flicker) maps on a two-tailed dependent-samples T-Test, two positive cluster frontally distributed (p= .009; p = .01) and a posterior negative cluster survived (p<.01) cluster-based correction for multiple comparisons (Maris & Oostenveld, 2007) (alpha = .025). Although it was partially pointed by

the previous power analysis (*Figure 8*) on the topography of the flicker effect, this last result suggests that information about the cognitive and perceptual representations during encoding can be discriminated from the decoding maps.

The present study aimed to track offline episodic memory reactivation through the re-emergence of the frequency-tags used during encoding. Consequently, the first prerequisite is evidence for exact effect of the flicker frequency during encoding. From the analyses conducted upon encoding, it is straightforward to see that the oscillatory entrainment was specific across the topography (*Figure 7* and *Figure 8*) and the frequency patterns (*Figure 8*).

3.6. Evidence for sensor-space offline reactivation

The direct contrast of post vs pre-encoding reactivation indexes for deep and shallow conditions (Figure 10) yielded a significant positive cluster for the deep reactivation ($p = 0.002$), but not for the shallow after correcting the p values for multiple comparisons using Bonferroni method ($p = 0.025/2$).

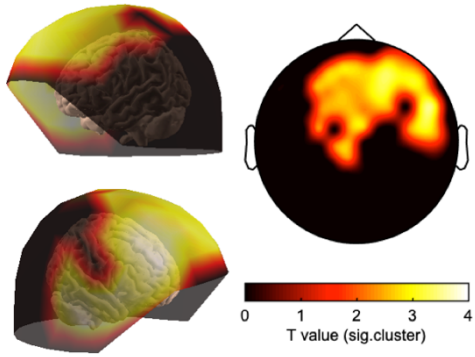

Figure 9. Sensor-space offline reactivation after deep encoding. The T-Test from the comparison between post- and pre- deep encoding power revealed a broad positive cluster over anterior sites of the helmet ($p<.01$). 3D and 2D topoplots show the t-values over the sensors belonging to the significant cluster.

As shown in *Figure 9*, results revealed that anterior sensors distinguished between the post and pre offline reactivation of deeply encoded items ($p <.01$), arguably due to the post-encoding reactivation and re-emergence of the entrained frequencies. However, a relative post-

encoding increase may also be produced by a generalised and non-specific power increase across the spectrum after the flicker stimulation. If so, the here described reactivation would be a by-product of this increase. Although this scenario would have also produced significant effects on the shallow reactivation contrast, a critical control entails testing the same procedure over a non-entrained frequency (*see Materials and methods*). This control analysis centred at 10.3Hz (9.8-10.8Hz) did not yield any significant effect suggesting that the spontaneous reactivation found here is specific to the experimental manipulations.

3.7. Prefrontal and mediotemporal regions track the reactivation of deeply encoded items.

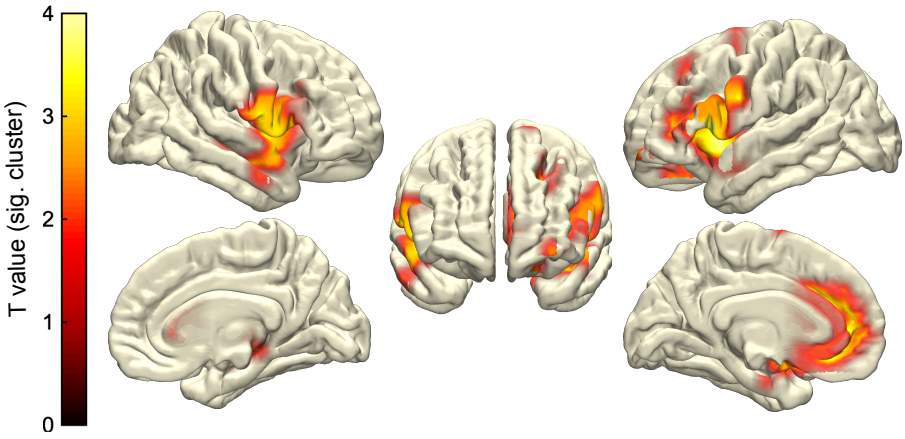

Figure 10. Source reconstruction of the deep offline reactivation effect. Significant clusters resulting from the contrast of post- vs pre- deep encoding offline power. Maximal effects were found over the left mPFC, bilateral inferior frontal gyrus and the left hippocampus.

As shown in *Figure 9*, the sensor-level reactivation was clearly localised over anterior sites of the helmet. The limited available electrophysiological evidence has revealed a central role of medio-temporal and prefrontal regions (Schreiner et al., 2018); however, it is unknown whether the entrained frequencies can track the reactivation supported by these regions. With the aim of testing whether reactivation reflects the engagement of medio-temporal and prefrontal areas, the deep reactivation effect observed at the sensor-space was projected onto the

source-space. As expected from sensor-space results, the direct contrast of post vs pre deep encoding offline periods revealed two significant clusters ($p < .01$ and $p = .02$) surviving cluster-based correction for multiple comparisons across source locations (Maris & Oostenveld, 2007). The set of regions that emerged (*Figure 10*) strongly converges with the consolidation network, showing a maximal post-encoding power increase over the left mPFC and the left and right inferior frontal gyrus. The careful inspection of the source-space maps also revealed a less prominent contribution of bilateral MTL structures, especially in the left anterior hippocampus. This result strongly suggests that the re-emergence of the entrained frequencies enable to track spontaneous reactivation of deeply encoded items during waking rest, mainly over regions of the consolidation circuits.

3.8. Post-encoding offline reactivation is related to subsequent associative memory performance

Lastly, out experimental paradigm (*see Figure 5*) included a retrieval stage after the post-encoding offline period that evaluated two levels of recognition memory: item and associative memory. Whereas the first level only implies an old/new decision (item memory), the second level entailed a more difficult retrieval scenario (*see Chapter 1*) since it demanded the recollection of the paired associated (associative memory). fMRI evidence has already proven that spontaneous offline reactivation in medio-temporal lobe structures has an impact on the subsequent memory (Staresina et al., 2013). However, two critical questions remain unclear: (i) whether the consolidation network as a whole –including regions outside the hippocampus– contribute to later memory performance; and (ii) since BOLD changes provide an indirect measure of brain activity, whether the reactivation reflected on the oscillatory entrainment re-emergence is also linked to behaviour.

It is well established that associative memory is more reliant on the hippocampus than item memory (Mayes et al., 2007; Yonelinas, 2002). Moreover, episodic memory consolidation has been previously linked to hippocampus-dependant processes (Frankland & Bontempi, 2005; Mölle & Born, 2011). Therefore, given the high HITs rate (mean = .88, SEM = .02) yielded by the deep encoding task (*Table 2*) a more stringent

behavioural measure to address the impact of reactivation on performance might be the recollection of the paired associate (AM; mean = .55, SEM = .06).

We thus obtained the post-encoding offline power increase by averaging the power of the source locations belonging to the significant clusters revealed in the previous analysis (*Figure 10*) and subtracting the equivalent mean pre-encoding offline power. This procedure was repeated for each subject, and the resulting values were then correlated with individuals' AM performance. The Pearson correlation showed a significant positive relationship between reactivation and AM performance (*rho* = .56, p= .03), suggesting that those participants with higher offline reactivation rates also performed better on the subsequent associative memory task (*Figure 11*). This study showed for the first time that consolidation can be tracked not only by the reactivation of spatial patterns as fMRI suggested, but also by the reactivation of oscillatory patterns. Furthermore, these results extend the previous fMRI evidence of the boosting effect of spontaneous reactivation on memory performance (Staresina et al., 2013), now showing that not only medio-temporal structures but also the mPFC among other frontal areas have a role on consolidation processes of recent memories.

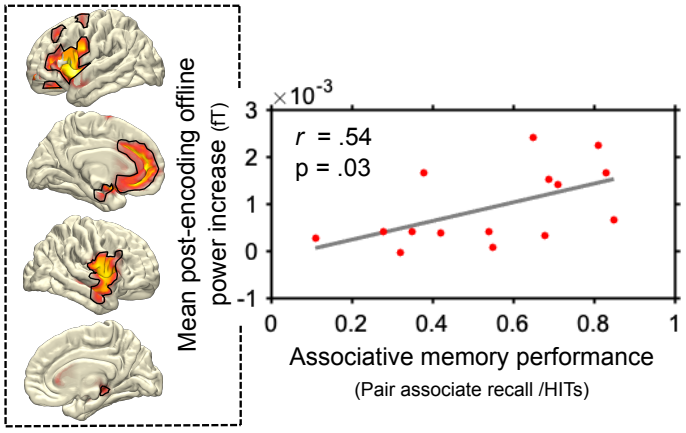

Figure 11. The role of offline reactivation in associative memory performance. Offline reactivation, quantified as the mean post-encoding relative power increase over the discriminant areas (significant cluster) predicted later associative memory performance.

4. Discussion

Rodent studies have provided compelling evidence that the hippocampus replays recently acquired experiences during wakefulness resting periods. There is also accumulating evidence that the consolidation process may engage other structures outside the hippocampus, such as the mPFC (Barker & Warburton, 2008). The neural activity that takes place on these regions seems to have a causal role since its blockade disrupts later memory performance (Tse et al., 2011). Although human evidence is restricted to fMRI and the reactivations of spatial patterns, the results are highly consistent with rodent literature, since evidence of individual item reactivation have been already found with a direct link to a subsequent memory enhancement (Staresina et al., 2013). Electrophysiological evidence might provide further insight into the neural mechanisms underlying awake reactivation; however, arguably due to the difficulties of tracking spontaneous reactivation without a cue or a trigger, this evidence is still lacking. We attempted to overcome this difficulty by capitalising on the property of the oscillatory entrainment to produce specific power changes in the M/EEG signal associated to different experimental conditions (Cohen, 2014). In other words, the main goal was to address whether the oscillatory patterns can track episodic memory reactivation during waking rest.

The present results reveal that oscillatory entrainment can be exploited to track spontaneous –uncued– offline reactivation during periods of waking rest. Specifically, the use of levels of processing during encoding (Craik & Lockhart, 1972) enabled to capture frontal MEG power changes associated to the specific entrained frequencies after deep processing, but not after shallow processing (*Figure 9*). The source reconstruction pinpointed this post-encoding deep reactivation over the left mPFC, bilateral inferior frontal lobe and MTL regions (*Figure 10*). Our results demonstrate that spontaneous offline reactivation during wakefulness over this set of regions predicts associative memory performance in humans (*Figure 11*).

We note that the power changes elicited by the experimental frequency-tags were highly specific both during encoding (*Figure 7* and *Figure 8*) and offline periods (see control analysis results at *Evidence for*

sensor-space offline reactivation). Power entrainment during encoding was centred at posterior sensors –as previously reported in visual perception studies with frequency-tags within the alpha range (Keitel, Quigley, & Ruhnau, 2014)–; however, during offline periods the reactivation effect was found over frontal sites of the helmet (Figure 10). Therefore, it is highly improbable that our effects reflect some sort of reverberation after the flickering visual stimulation. To make sure that this was not the case, we repeated the analysis to quantify offline reactivation with a non-entrained (9.8-10.8Hz) frequency equidistant to the experimental flicker frequencies and no significant effect was found. To further link memory reactivation with behaviour, we addressed reactivation separately for post-deep and post-shallow encoding offline periods (*see Materials and Methods*). Given that only one condition (deep task) yielded significant offline reactivation effects and the power measures came from the same post-encoding periods for both conditions, a spurious power change unrelated to the entrainment can thus be discarded.

Systems consolidation refers to the time-dependent processes involved in reorganising long-term memory representations after encoding. Although the first proposals of systems consolidation were focused on the role of the hippocampus, recent views posit that this reorganisation is done over distributed brain circuits (Dudai et al., 2015). Compelling evidence in humans has shown that hippocampal-neocortical BOLD functional connectivity within the first minutes after encoding can predict memory performance (Tambini & Davachi, 2013; Tambini et al., 2010). Among the neocortex, recent evidence in animals (Tse et al., 2011) demonstrated the causal role of the mPFC, emerging as a key region within the consolidation network. In humans, the role of the mPFC on consolidation has been inferred from its engagement on remote memories retrieval (Takashima et al., 2006) and sleep (Gais et al., 2007; Sterpenich et al., 2009). Special mention is deserved by a recent multi-day fMRI study (Tompary, Duncan, & Davachi, 2017) that exploited multivariate pattern analysis to demonstrate that neural patterns of arguably re-structured memories were found over the mPFC and the hippocampus only for remote memories (after a week). Interestingly, their data showed a non-significant trend of post-encoding connectivity increase in this circuit during the immediate resting periods after the study phase. Although they interestingly suggested an early active consolidation

mechanism for re-structuring certain memories, their results were not conclusive.

Mapping the sensor-space reactivation for post-deep encoding offline periods (*Figure 9*) onto the source space, we found that reactivation not only emerged from the medial temporal lobe but also was maximal in the left mPFC and the inferior frontal gyrus (*Figure 10*). We noted that this set of regions remarkably coincided with animal and human studies, particularly with the above commented fMRI study from Tompary & Davachi (2017); however, we are cautious when interpreting deep sources reconstructed from the MEG signal. Worthy of note, however, is the accumulating evidence indicating that hippocampal signals can be reliably detected with MEG (for a review, see Pu et al., 2018). That said, the topography of the present data extend the previous imaging findings, providing direct evidence that prefrontal-hippocampal activity can happen during waking rest in humans early after encoding.

A striking result was the lack of significant reactivation during the resting periods following the shallow encoding task. As levels-of-processing framework predicts, this task yielded poor subsequent memory performance (mean paired associate recall = 14%; *see Table 2*). Although caution is warranted when interpreting negative results, we note that the failure to find offline effects after a task with poor subsequent memory is congruent with the results of preceding imaging studies (c.f. Tambini et al., 2010). The criteria by which memories are reactivated seems not to be straightforward, since recent fMRI findings tracking individual items have shown higher reactivation rates in the hippocampus for weaker memories (Schapiro, McDevitt, Rogers, Mednick, & Norman, 2018), it remains to be determined how consolidation mechanisms unfold according to the memory quality. Thus, to assess whether the magnitude of the prefrontal-hippocampal reactivation was linked to subsequent memory performance, we correlated post-encoding offline reactivation after the deep task with the more demanding retrieval task of our paradigm, i.e., the proportion of paired associate recall (AM). This analysis revealed that the magnitude of the reactivation within the prefrontal-hippocampal circuit during rest predicts individual differences in later recollection (*Figure 11*). This finding adds to a growing body of evidence of the boosting effect of offline reactivation on memory during wakefulness.

Although the reactivation topography (*Figure 10*) was consistent with systems consolidation proposals (Frankland & Bontempi, 2005), and increasing evidence is backing the assumption that the reorganisation of long-term memory may take place during the first moments after the study phase (Tompary, Duncan, & Davachi, 2015; Tompary et al., 2017; Vilberg & Davachi, 2013), some studies have raised the possibility that offline activity during wakefulness may not be directly related to consolidation (Ben-Yakov, Eshel, & Dudai, 2013). The here analysed offline periods lasted 60 seconds which may be a long period for encoding processes, but future clarification between consolidation and other peri-encoding processes is to be done. The reactivation effect we observed here was maximal over prefrontal regions like the mPFC, whose implication in the transformation of long-term memories is twofold. First, mPFC role on consolidation is inferred by its engagement during the retrieval of remote episodic memories (Sterpenich et al., 2009; Takashima et al., 2006; Tompary et al., 2017) and sleep-dependent processes (Gais et al., 2007; Meeuwissen et al., 2011; Sterpenich et al., 2009). Second, a growing body of evidence suggests that the mPFC is also involved in the integration of memories at different stages of the processing: encoding (Kuhl, Shah, Dubrow, & Wagner, 2010; Schlichting & Preston, 2016), consolidation and retrieval (Tompary et al., 2017; Tse et al., 2007, 2011; Zeithamova & Preston, 2010). For example, it is recruited when incoming memories are related to the existing knowledge (Tse et al., 2011) or when there are overlapping features (Tompary et al., 2017) or shared content (Sweegers & Talamini, 2014; van Kesteren, Fernandez, Norris, & Hermans, 2010). Critically, we found a prefrontal-hippocampal offline reactivation immediately after encoding in a way that these memories cannot be considered remote which might have implications in our current models of consolidation. Since most of the human evidence is restricted to fMRI, one possibility is that, as found in the rodent hippocampus, the reactivation of recent memories across the prefrontal-hippocampal circuit may also happen in a transient manner (György Buzsáki, 2015) making it difficult to be captured with fMRI. On the other hand, in the light of rodent studies (Tse et al., 2011) that demonstrated that consolidation is accomplished rapidly by the mPFC if the incoming information can be integrated within the schematic knowledge, it is possible that the deep encoding task of our paradigm that explicitly asked

the participants to integrate both objects, may have triggered this route. However, the mPFC-hippocampal interaction might implicate a complex trade-off between the integration and the contextual details, since reactivation correlates with the paired-associate recall, a task that demands to access to the episodic details of the representation. Further electrophysiological studies are needed to reveal whether mPFC is engaged for recent memories as well as for remote memories in humans or its engagement is due to the necessity of integration.

One objective of this study was to use oscillatory entrainment to track spontaneous memory reactivation. This experimental manipulation was done under the assumption that memories would be 'tagged' with a specific frequency that would later re-emerge in the form of power changes if reactivation happened during the offline periods. Specifically, we found a power increase after a deep encoding task relative to a pre-encoding baseline. Subsequent source reconstruction of reactivation revealed the contribution of mPFC, inferior frontal gyrus and medio-temporal areas which compares well with previous consolidation evidence. Further, the post-encoding power increase in this set of regions related to the paired associate recall across participants. Since we only found reactivation after a deep encoding task, a challenging question for future studies will be to explore the criteria by which memories are reactivated during waking rest and what is the functional role of the mPFC and the hippocampus in the consolidation of recent memories.

5. Conclusion

To summarize, our findings extend previous evidence (Wimber et al., 2012) showing that oscillatory entrainment can finely tag memories to capture its later reactivation. Our results revealed not only mPFC-hippocampal reactivation of recent memories during wakefulness in humans, but also showed preliminary evidence of its functional role in offline memory consolidation.

Chapter 5

Experimental study II: Retrieval

Alpha rhythms reveal when and where memories are retrieved

Highlights

- Alpha rhythms distinguish between different retrieval outcomes
- Alpha power time courses track familiarity and recollection
- Alpha source reconstruction tracks the fMRI core recollection network
- MEG alpha power may unify ERP and BOLD-fMRI recollection findings.

1. Introduction

Investigation of the neural mechanisms supporting memory retrieval has been ignited by EEG studies revealing a left posterior 'old/new' effect, i.e., a difference in slow event-related potentials (ERPs) over left posterior sensors unfolding between 500 and 1000 ms after cue onset (Sanquist et al., 1980; for a review see Rugg and Curran, 2007). In parallel, fMRI studies have consistently shown a core brain network, featuring parietal and medial temporal regions, differentially engaged during successful recollection (Hayama et al., 2012; Rugg & Vilberg, 2013). However, due to inherent limitations of both methods (relatively poor spatial resolution of scalp ERPs, poor temporal resolution of fMRI), it is unclear whether the cue-evoked ERPs reflect engagement of the core recollection network and whether engagement of the fMRI network is temporally linked to the moment of recollection, as opposed to pre-

stimulus/preparatory deployment of attention or post-retrieval monitoring (Levy, 2012; Carlo Sestieri, Shulman, & Corbetta, 2017). Direct intracranial recordings would provide the desired temporal and spatial resolution, but comprehensive coverage of both parietal and mediotemporal areas is rare and advanced retrieval paradigms (sensitive to familiarity and recollection) are challenging to conduct with patients (Foster, Rangarajan, Shirer, & Parvizi, 2015; Gonzalez et al., 2015).

That said, one viable means of integrating the strengths ERP and fMRI recordings might be the examination of oscillatory patterns in the alpha frequency band (8-12 Hz). On the one hand, modelling and empirical work suggests that slow ERPs might reflect asymmetric amplitude fluctuations in the alpha band, such that e.g. oscillatory peaks become more pronounced than troughs over time (Mazaheri & Jensen, 2008). On the other hand, simultaneous EEG-fMRI recordings have revealed a strong link between blood-oxygenation-level-dependent (BOLD) signal increases and decreases in alpha power (Laufs et al., 2003; Meltzer, Negishi, Mayes, & Constable, 2007; Moosmann et al., 2003; Scheeringa et al., 2011). We thus hypothesised that alpha desynchronization not only differentiates between recollection- and familiarity-based retrieval in the time domain (from ~500 ms onward), but that this effect spatially maps onto the core recollection network, thus pinpointing its purported role in peri-stimulus retrieval.

Capitalising on the increased spatial resolution of Magnetoencephalography (MEG) over EEG (Baillet, 2017; Lopes da Silva, 2013), we employed an associative recognition paradigm (Figure 1) in which participants (n=15) indicated whether a given word was (i) new, (ii) old but they could not remember the paired associate, or (iii) old and they also remembered the paired associate. In the latter case, a second screen appeared in which participants indicated which of three first-and-last-letter combinations corresponded to the target paired associate.

2. Materials and Methods

Data, participants, behavioural analysis, experimental procedure, MEG recordings and preprocessing were the same as in the study of the *Chapter 3*. In this section only the particular aspects of interest to this study will be addressed.

2.1. Experimental procedure

A schematic diagram of the whole experimental paradigm can be found in *Figure 5*. For the sake of clarity, further details of the relevant phase of this experiment (retrieval) will be provided (*Figure 12*).

During the retrieval block, participants were presented with one randomly chosen word from each of the 28 previously seen pairs as well as 14 novel nouns. First, participants indicated if the word was (i) old and they also remembered the paired associate, (ii) old but they could not remember the paired associate, or (iii) new. The response was collected with a single button press and the word remained in the screen during 4 seconds regardless of the participant's response. When the first option was selected, a validation screen of 2 seconds of duration appeared and the participants had to choose which of three first-and-last letter combinations corresponded to the remembered paired associate. This two-step structure served as a means of objective validation while holding the stimulus display and response options constant for the initial 4 seconds of the trial. Preceding each trial, a fixation cross was displayed during a jittered intertrial interval of 850 to 1150ms.

For subsequent analyses, the following three conditions of interest were defined: Associative Memory (AM; trials in which participants indicated they recognized an old word and recalled the paired associate, followed by a correct response during verification); Item Memory (IM; trials in which participants indicated they recognized an old word but did not recall the paired associate) and Correct Rejection (CR; trials in which participants correctly identified new items). In order to restrict our analyses to correct memory trials, we excluded Misses (trials in which old items were incorrectly identified as new), False Alarms (trials in which new items were incorrectly identified as old) and trials in which participants first indicated they recalled the word plus its paired associate but then gave an incorrect response during verification.

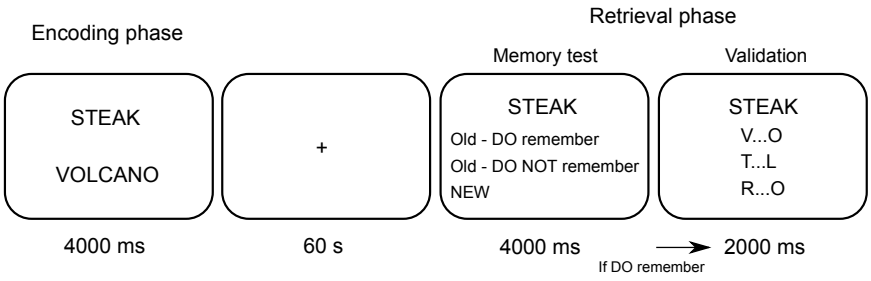

Figure 12. Experimental procedure of the study II. During the study phase ('encoding'), participants saw word pairs under deep or shallow processing tasks. During the subsequent test phase ('retrieval'), one word of the previously presented pairs was shown, intermixed with unstudied new words ('lures'). Participants indicated with one button press whether they thought the given word was new, the word was old but they did not remember the paired associate (item memory, IM) or the word was old and they recalled the paired associate. In the latter case, a second validation screen appeared to validate recall accuracy, providing three first-last letter combinations of which one corresponded to the target association. Analyses focused on correct identification of lures (correct rejection, CR), correct identification of old words without recalling the paired associate (item memory/familiarity; IM) and correct identification of old words along with correctly recalling the paired associate (associative memory/recollection; AM).

2.2. MEG preprocessing

Preprocessing was carried out following the same procedure as in Chapter 3. After artifact rejection, an average of 15% (range: 1–60 %) of all trials were discarded across participants. The AM condition contained an average of 55 trials (range: 10-151), the IM condition contained an average of 74 trials (range: 14-135) and the CR condition contained an average of 79 trial (range: 30-109).

2.3. Quantification and statistical analysis

2.3.1. Sensor space time-frequency analysis and statistics

Frequency decomposition was obtained for each trial using Fast Fourier Transform (FFT) based sliding window analysis, progressing in 50 ms steps. The window length was optimised for each frequency from 1 to 80 Hz, with a minimum of 200 ms and 5 cycles (for instance, using 500 ms/5 cycles for 10 Hz, and 200 ms/6 cycles for 30 Hz). The data in each time window were then multiplied with a Hanning taper before

Fourier analysis. The power values were obtained for the vertical and horizontal component of the estimated planar gradient and then combined. Finally, the resulting power maps were normalised by z-scoring the data for each channel, using mean and standard deviation of power from -0.5 to 2s across all retrieval trials.

To assess, in one step, which time- and frequency bins differentiate between the three memory conditions across channels, we conducted a one-way repeated measures ANOVA from -0.5 to 2s and from 1-80 Hz, using the factor Memory (CR, IM, AM). To correct for multiple comparisons across time, frequency and channels, we used a non-parametric cluster-based permutation test (Maris & Oostenveld, 2007), setting the cluster alpha at $p = .025$.

The 10-12Hz power time courses in Figure 3 were derived by averaging across the five left parietal sensors showing the maximal effect within the significant cluster (*Figure 13A*, dashed red square).

2.3.2. Source reconstruction

To estimate the underlying brain activity for the alpha band (8-12 Hz) effects found at the sensor level, we performed source reconstruction from -0.5 to 2 s, following the same procedure as in *Chapter 4*. The common filter to ensure reliable comparison between conditions was constructed as follows: the spatial filter's coefficients were obtained from the average covariance matrix from all CR, IM and AM trials and then this filter was multiplied with each condition separately (note that the same pattern of results emerged when using only IM and AM trials for filter construction). Because we were interested in the origin of our effects within the alpha range and lcmv-beamforming filters are most precise for narrowly-filtered data (Van Veen, van Drongelen, Yuchtman, & Suzuki, 1997), filters were derived for artifact-free data from 8 to 12 Hz. The final output consisted of a time series estimate per source location, condition and subject.

2.3.3. Source space time-frequency and statistics

Spectral analysis was performed on the reconstructed signal in the same way as in sensor space but restricted to the alpha frequency band (8-12 Hz). There are several ways to avoid a beamforming bias towards the

centre of the head: although any noise bias would be the same for all conditions, we additionally baseline-corrected each condition before performing any contrast. Specifically, we computed the relative change of the power estimates using a baseline time window from -0.4 to -0.2 s.

To statistically test the sensor-space recollection effect (AM vs. IM) in source space, we averaged source time series from 10-12 Hz (*Figure 14A*) and from 1 to 1.5 s and conducted a dependent-samples T-Test (*Figure 15*). To correct for multiple comparisons across source locations, we used a non-parametric cluster based permutation test with an alpha = .025.

3. Results

3.1. Behavioural results

Focusing on correct memory outcomes, our three conditions of interest were (i) correct rejection of new words (CR), (ii) correct identification of old words, without recalling the paired associate (familiarity/item memory, IM) and (iii) correct identification of old words along with correct recall of the paired associate (recollection/associative memory, AM). We used a levels-of-processing manipulation during encoding (Craik & Lockhart, 1972) to yield sufficient numbers of both IM and AM trials (*see Materials and Methods*).

	Proportion		Reaction times (s)	
	Mean	SEM	Mean	SEM
Correct rejections	0.87	0.03	1.49	0.06
Hits	0.72	0.04	1.76	0.07
Associative memory	0.45	0.05	1.53	0.07
Item memory	0.55	0.05	1.92	0.09

Table 3. Retrieval test accuracy and reaction times. For Correct rejections and Hits, proportion denotes proportion of all new (112) and old (224) trials.

As shown in *Table 3*, this had the desired effect of producing sufficient trial numbers for our conditions of interest (*see Materials and methods*), particularly for both IM and AM trials, allowing us to probe both

familiarity- and recollection based recognition memory. So, for subsequent analyses we collapsed deep and shallow encoded trials.

The overall rate of HITs (collapsing IM and AM) minus false alarms was 0.59, indicating high levels of recognition memory. Reaction times (RTs) differed significantly across our conditions of interest: RTs for Hits were significantly longer than for CR (t_{14} = 3.26; p = .005), and for IM compared to AM (t_{14} = 3.87; p = .001).

3.2. Alpha rhythms track time courses of familiarity and recollection

Given the RT distribution across trial types (*Table 3*), we restricted our sensor space analysis to the first 2 seconds after cue onsets (longest average RT of 1.92 s). To identify - in one step - time points, frequencies and sensors modulated by memory outcome, we first conducted a repeated-measures ANOVA with the factor Memory (CR, IM, AM) on time-frequency representations (TFRs) across sensors. Results showed a significant effect surviving cluster-based correction for multiple comparisons (Maris & Oostenveld, 2007) (p < .001).

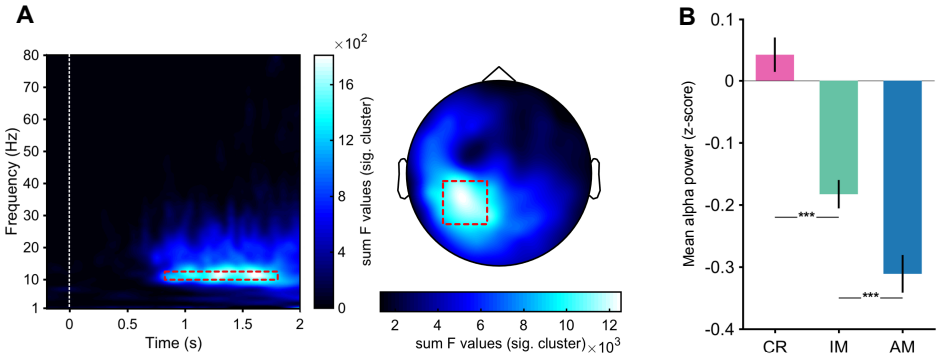

Figure 13. Sensor space results. (A) ANOVA results for the comparison of CR, IM and AM TFRs revealed a significant cluster from .8-2 s at left posterior sensors with a peak at 10-12 Hz. TFR plot (*left*) depicts the sum of F-values across all significant sensors of the cluster. Topoplot (*right*) shows the sum of F-values across all significant time/frequency bins of the cluster. (B) Mean (+/-SEM) alpha power for each memory condition collapsed across left posterior sensors from .8-1.8 s in the 10-12 Hz frequency range (red dashed boxes in A), showing a relative power decrease ('desynchronization') modulated by memory outcome. ***: p < .001, paired samples t test

As shown in *Figure 13A*, the effect was centred at left posterior sites, spanning a time window of .8-2 s and a frequency range from 8-20 Hz, with a distinctive peak from 10-12 Hz (alpha frequency range). Extracting

the corresponding power values for the three memory conditions, post hoc pairwise tests revealed a stepwise decrease in alpha power from CR to IM ($t_{(14)}$=-8.41, p < .001) and from IM to AM ($t_{(14)}$=-4.75, p < .001) (*Figure 13B*). These results extend previous findings of left posterior alpha power distinguishing between correctly recognised old and new items (Hanslmayr et al., 2012), now showing that it further distinguishes between item and associative recognition memory.

Do item- and associative memory effects in the alpha band unfold at different latencies, tracking the relative delay of recollection with respect to familiarity-based recognition (Yonelinas, 2002)? To address this question, we examined the time courses of alpha power at left posterior sensors for CR, IM and AM. As shown in *Figure 14A*, an item recognition/familiarity effect (IM vs. CR) emerged at 600ms post cue onset. Next, with a delay of ~200 ms, an associative recognition/recollection effect emerged as a significant decrease in alpha power for AM relative to IM.

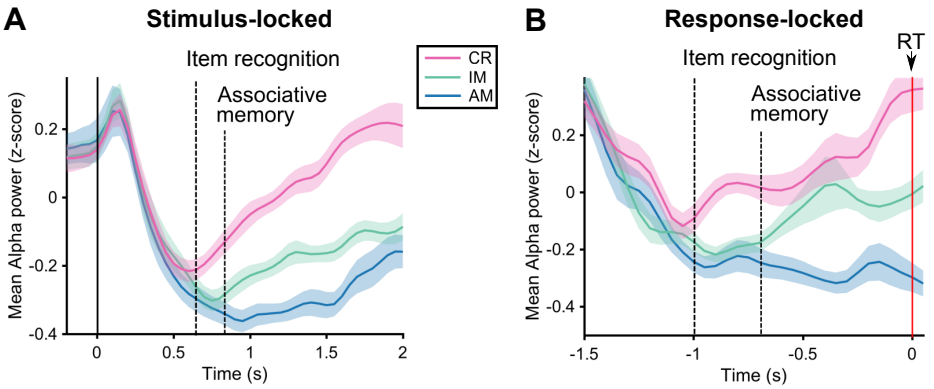

Figure 14. Alpha power (10-12 Hz) time courses, collapsed across left posterior sensors (cf. Figure 2A). (A) Stimulus-locked and (B) Response-locked averages across participants (+/- SEM). Dashed vertical lines highlight onsets at which familiarity-based (IM vs. CR) and recollection-based (AM vs. IM) recognition effects unfold.

This progressive, step-wise alpha power decrease suggests that alpha desynchronization directly tracks neural and cognitive processes giving rise to familiarity- and recollection-based recognition. However, to ensure that our effects do not reflect post-retrieval processes (e.g., idling or monitoring, *see Discussion*), we repeated the timecourse analysis with response-locked rather than stimulus-locked data, thereby accounting for different response latencies across memory conditions (*Table 3*). Indeed,

results confirmed that the differential familiarity- and recollection effects unfolded well before the behavioural response: The familiarity effect (IM vs. CR) emerged ~1000 ms prior to the response, followed by a recollection effect (AM vs. IM) ~ 700 ms prior to the response (*Figure 14B*).

3.3. Alpha rhythms track engagement of the core recollection network

As shown in *Figure 13*, the sensor-level alpha effects were most pronounced over left posterior sites. While this topography is well in line with a host of ERP studies revealing a left posterior recognition memory effect (Sanquist et al., 1980; for a review see Rugg and Curran, 2007), more recent fMRI investigations of recognition memory have consistently revealed a 'core-recollection' network, including left parietal and medial temporal regions. However, it is unclear from fMRI studies whether that core recollection network indeed reflects processes leading up to the phenomenology of recollection ('peri-retrieval' (C. Sestieri, Corbetta, Romani, & Shulman, 2011)) or whether it reflects post-retrieval processing (Vilberg & Rugg, 2008; Wagner et al., 2005) or even pre-stimulus attention effects (Cabeza et al., 2008). In the next step, we thus set out to source-localise the peri-retrieval alpha patterns we observed at the sensor level in order to test whether they reflect engagement of the core recollection network.

We focused our source level analysis on the 1 to 1.5 s post-stimulus time window to best capture recollection-specific processes (Figure 3B) (*see Materials and methods*). The direct contrast of AM vs. IM revealed a significant cluster ($p < .001$) with a maximal alpha power decrease for AM in left posterior parietal cortex (lPPC; including superior and inferior parietal lobule, angular gyrus and precuneus), left lateral temporal cortex (lLTC) as well as left medial temporal lobe (lMTL) (*Figure 15*). This set of brain regions strongly converges with the core recollection network identified in fMRI studies (Hayama et al., 2012; Rugg & Vilberg, 2013).

4. Discussion

Over the last decades, the question of when and where recollection processes unfold has been independently tackled by electrophysiological (EEG) and neuroimaging (fMRI) investigations, respectively. EEG research has revealed that recollection is hallmarked by a slow and sustained event-related potential (ERP) over left posterior sensors emerging between 500-1000 ms, after an initial familiarity or item recognition signal (Yonelinas, 2002; Rugg and Yonelinas, 2003) . However, given the spatial ambiguity of ERPs, the contributing brain regions have remained largely unknown.

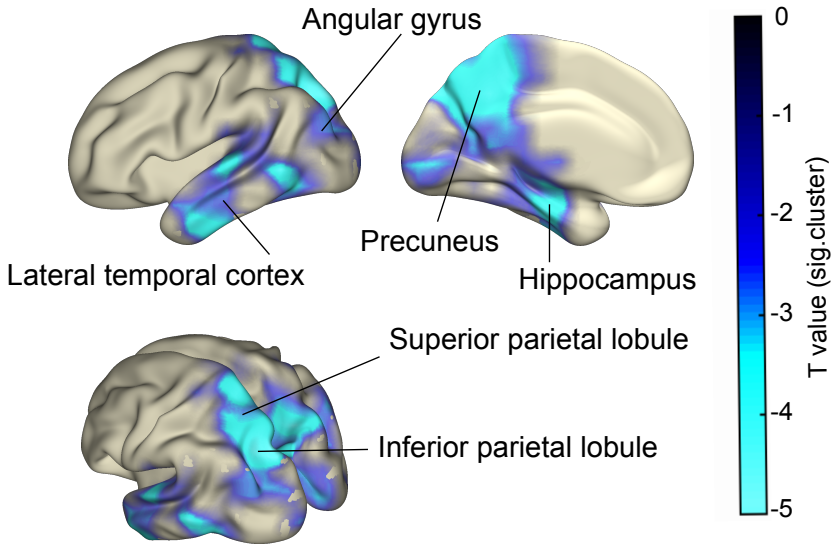

Figure 15. Source reconstruction of the Recollection effect**.** Significant cluster resulting from the contrast of AM vs. IM in the 10-12 Hz alpha band. The relative alpha power decrease for AM mirrors the core recollection network identified in fMRI studies. Labelling of brain regions is based on the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002).

Conversely, fMRI research has consistently revealed a set of brain regions particularly engaged during recollection-based recognition memory, commonly referred to as the 'core recollection network' (Hayama et al., 2012; Rugg & Vilberg, 2013). However, due to the relatively poor temporal resolution of fMRI, it has remained unclear

exactly which of the manifold processes linked to recollection (e.g., preparatory states, cue perception, retrieval effort, post-retrieval monitoring) these regions actually support. Here, we report that alpha power desynchronization unifies these lines of research, integrating both the temporal and spatial profiles of recollection via a single physiological mechanism.

Despite the long history of M/EEG studies on recognition memory (Sanquist et al., 1980; for reviews, see Mecklinger, 2000; Rugg and Curran, 2007), only a few have examined oscillatory patterns related to different memory outcomes (Burgess & Gruzelier, 2000; Khader & Rösler, 2011; Michelmann et al., 2016; Vogelsang, Gruber, Bergström, Ranganath, & Simons, 2018; Waldhauser et al., 2016), albeit without explicitly distinguishing recollection- from familiarity-based recognition. By assessing item- and associative memory, our paradigm allowed us to directly probe the oscillatory mechanisms that support these qualitatively different memory signals (*Figure 12*). As shown in *Figure 13*, results revealed that left posterior alpha desynchronization not only tracked simple old/new recognition memory (CR vs. IM/AM), but further distinguished between familiarity- and recollection-based recognition (AM vs. IM). Indeed, time course analyses (*Figure 14A*) confirmed the temporal offset between an earlier familiarity signal (starting at ~600 ms after cue onset) followed by a later recollection signal (starting at ~800 ms after cue onset) (Rugg & Yonelinas, 2003; Yonelinas, 2002). In sum, we show that left posterior alpha desynchronization tracks familiarity- and recollection-based recognition both in amplitude and latency. Considering the potential link between amplitude fluctuations in the alpha band and sustained ERP/ERF deflections (Mazaheri & Jensen, 2008), our data raise the possibility that at least some of the classic ERP recognition effects reflect condition-specific differences in alpha power.

In a separate line of research, fMRI studies on recognition memory have consistently shown engagement of a particular set of brain regions in recollection-based memory, including lateral/medial parietal and temporal regions. The robustness of these regions' engagement across numerous paradigms has given rise to the notion that they represent a 'core recollection network' (Rugg & Vilberg, 2013). However, given the relatively poor temporal resolution of fMRI, it has been challenging to pinpoint the exact cognitive (sub)processes during recognition these

regions support. Accordingly, while some accounts posit that this network represents informational content during retrieval (Johnson et al., 2013; Rugg & Vilberg, 2013; Thakral et al., 2017; Vilberg & Rugg, 2014), others highlight – particularly regarding parietal contributions – pre-retrieval (Cabeza, 2008), peri-retrieval (Haramati, Soroker, Dudai, & Levy, 2008; Shimamura, 2011; Wagner et al., 2005) or post-retrieval (Ciaramelli et al., 2010) operations (for a review see Levy, 2012; or Sestieri et al., 2017). Projecting our sensor data into source space, we found a striking overlap of our alpha power recollection effect with the core recollection network (*Figure 15*). Not only did the relative alpha desynchronization for AM map onto left lateral parietal cortex (angular gyrus, superior and inferior parietal lobule), medial parietal cortex (precuneus; see also (Bergström, Henson, Taylor, & Simons, 2013)) and lateral temporal cortex, but source reconstruction also implicated left hippocampus in the recollection effect. The topographical correspondence of our alpha power decreases with BOLD increases commonly found in fMRI studies on recognition memory adds to a number of EEG-fMRI studies showing a tight coupling of these two measures (Laufs et al., 2006) and suggests that alpha power can, at least in some cases, be used as a time-resolved proxy for BOLD activation. Accordingly, the yoking of our alpha desynchronization effects with the fMRI recollection network now provides critical insights into this network's temporal profile. As shown in *Figure 14*, recollection effects clearly unfolded after cue onset (*Figure 14A*) but well before the mnemonic decision (*Figure 14B*). Our results are thus most consistent with the idea that parietal and medial temporal lobe regions primarily contribute to peri-retrieval processes such as active memory search, the accumulation of mnemonic evidence and/or providing an 'episodic buffer' (Baddeley, 2000; Hayama et al., 2012; Rugg & Vilberg, 2013; Shimamura, 2011). The link between alpha power decrease and the accumulation of mnemonic evidence also aligns with a recent model suggesting that low frequency desynchronization reflects the amount of information represented by a given region (Hanslmayr et al., 2012; Hanslmayr et al., 2016) rather than mere activation (Pfurtscheller & Lopes, 1999) or disinhibition (Jensen & Mazaheri, 2010; Klimesch, 1996). Indeed, both the core fMRI recollection network (Hayama et al., 2012; Thakral et al., 2017) and late ERP sites (Vilberg, Moosavi, & Rugg, 2006; Wilding,

2000) have been shown to be sensitive to the amount of recollected information, analogous to the difference between AM and IM in our study.

It is important to note that other low frequency bands, particularly theta (4-8 Hz), have also been linked to memory processes. For instance, Osipova et al. (Osipova et al., 2006) found theta increases for HITs relative to CRs in an image recognition paradigm. Interestingly, though, this effect was localised to occipital cortex and already started 300 ms post cue onset. This raises the possibility that different functional networks involved in recognition memory are grouped by different frequency bands. Theta power increases have also been linked to hippocampal retrieval process in intracranial EEG (iEEG) recordings (Burke et al., 2014). Although that study employed a free recall rather than a recognition memory paradigm, theta power increases are markedly different from the hippocampal alpha power decreases we observed in our source-level data, and we note that caution is warranted when interpreting MEG effects in deep anatomical sources such as the hippocampus. That said, our findings add to a growing body of evidence of discernible MEG effects in the hippocampus (for a review, see Pu et al., 2018). More importantly, a recent iEEG study assessing associative vs. item memory found a hippocampal power decrease for recollection in the exact same time- and frequency range as observed here (10-12 Hz, starting at 800 ms) (Staresina et al., 2016). An important challenge for future studies will thus be to delineate the roles of hippocampal theta power increases vs. alpha power decreases in service of episodic retrieval.

5. Conclusion

To conclude, our neuroscientific understanding of recognition memory thus far relied upon separate lines of research capitalizing on either temporal (ERPs/ERFs) or spatial (fMRI) signal properties. This study now suggests that alpha rhythms represent a single oscillatory mechanism tracking where and when associative memory unfolds in space and time, linking engagement of parietal and medial temporal brain regions to recollection processes with millisecond precision.

Chapter 6

General discussion

1. General discussion

Reactivation is emerging as a central concept to understand episodic memory. This phenomenon ranged from the unconscious offline reactivation during resting periods to the conscious and full-blown recollection of vivid memories (Antony et al., 2017). Although neuroimaging techniques, mainly fMRI, have provided valuable insight into the brain regions that may be involved, the nature and temporal dynamics of different expressions of reactivation remain elusive. Two questions were thus posed in this thesis: how are our memories reactivated during different stages of mnemonic processing: consolidation and retrieval? Moreover, can we track the neural and cognitive mechanisms of reactivation through brain oscillations?

These questions were addressed capitalising on the spatiotemporal resolution of magnetoencephalography (MEG) and a novel implementation of oscillatory entrainment or frequency-tagging on a word-paired associates episodic memory paradigm. This approach enabled to get experimental data of the three main stages of memory processing: encoding, consolidation and retrieval. It thus attempted to offer a view of the fate of a memory representation since its creation, and its neural and behavioural correlates.

Concerning consolidation, we hypothesised that the entrained frequencies would spontaneously re-emerge during post-encoding offline periods. Our findings revealed that oscillatory entrainment can track reactivation during waking rest periods, particularly in those regions previously related to memory consolidation: mPFC and MTL. Moreover, this reactivation seems to be linked to hippocampus-dependent

memories, such as those deeply encoded, and can also predict subsequent memory performance. These data contribute to the current consolidation models, expanding the role of the mPFC-MTL circuit to spontaneously reactivated recent memories.

This was the first time that oscillatory entrainment was used to track memory processes during offline periods, so it may serve as a workable basis for future research on consolidation, or other cognitive processes in which it is difficult to pinpoint a trigger event. The careful inspection of our results may also lead to new questions. For example, we found a robust reactivation of deeply encoded trials; however, shallow processing also produced a non-significant reactivation. In the light of recent studies that found higher reactivation rates for weak memories (Schapiro et al., 2018), further research is needed to clarify the criteria by which memories are engaged into consolidation processes. Building on well-founded consolidation models (Frankland & Bontempi, 2005; Preston & Eichenbaum, 2013), we speculated that the here observed mPFC engagement might be due to the semantic and integration demands of the deep condition. It would be interesting to see whether shallow encoding recruits similar networks. This aspect falls under a critical and still unclear question: what is the functional role of neocortex and hippocampus during consolidation?

Our work did not address the question of the nature of offline reactivation: is it like the specific reinstatement produced at retrieval or is it different? We note that during encoding, the cognitive representation (deep vs shallow) was localised over frontal sensors, whereas the perceptual was more posterior. Comparing encoding topographies with the frontal distribution found during offline periods for the deep conditions, one may think that consolidation involves a certain reinstatement. However, the picture is still incomplete, because the coincidence of our source-space results with fMRI findings (Tompary et al., 2017) suggests that the re-emergence of the entrained frequency may be reflecting more general consolidation processes than specific reinstatement. A promising approach to disentangle the nature of reactivation may be the use of MVPA. The encoding (deep or shallow) or retrieval (AM, IM) topographical maps may serve to train the classifier. Then, if consolidation implied a reinstatement, the classifier would successfully discriminate between different conditions. However, it

would be the case that the spontaneous reactivation found here is reflecting a general consolidation network different to encoding and retrieval patterns. Therefore, the classifier might fail on discriminating between conditions based on the topographical maps.

Several findings reported disturbed resting-state activity in developmental (Cornew, Roberts, & Edgar, 2013), psychiatric disorders (Kim et al., 2014) and neurodegenerative diseases such as Multiple Sclerosis (Van Der Meer et al., 2013) or Alzheimer's disease (Fernández et al., 2006). Significantly, some of these disorders exhibit memory impairment and the changes in brain oscillations could be related to the disruption of memory processes such as consolidation.

The most important limitation of this study lies in the fact that we inferred memory reactivation from the re-emergence of the entrained frequencies so no mechanistic explanation may be derived from our findings. If the identification of spontaneous reactivation events linked to consolidation were perfected, we would be able to study its neural mechanisms directly (e.g., is there any brain oscillations that coordinates this reactivation?), such as it has been done in a recent cue-triggered MEG sleep study (Schreiner et al., 2018).

Despite these limitations, there are several reasons why we believe this study has a direct impact on our field. First, the mPFC-MTL reactivation (*Figure 10*) found here was highly consistent with consolidation models (Frankland & Bontempi, 2005; Preston & Eichenbaum, 2013). Second, there was a lack of evidence of spontaneous offline reactivation during waking rest using electrophysiological techniques in humans. Here, using a novel oscillatory entrainment paradigm, we demonstrated that reactivation can be tracked with MEG in those regions previously pinpointed with fMRI (Tompary et al., 2017). Lastly, the direct relationship found here between reactivation and associative memory performance (*Figure 11*), critically contributes to unveil the physiological meaning of awake reactivation beyond MTL structures (Staresina et al., 2013).

Chapter 2 provided a brief review of the central tenets of episodic memory from the perspective of psychology and cognitive neuroscience. A recurrent idea in many models and theories was the notion that episodic memories are the result of hippocampal-neocortical representations. Overall, the results of the first study are compatible with

this notion. Going one step further, recent views (Antony et al., 2017) proposed that retrieval may mimic offline reactivation, acting as a fast route of systems consolidation. From this point of view, retrieval may be considered as a mechanism for online reactivation. The review of the literature on retrieval revealed that our current understanding of this stage of the mnemonic processing is by far much more understood than consolidation. Among retrieval expressions, recollection entails the most detailed and vivid reactivation of prior experiences. This remarkable ability has been intensively studied during the last three decades (Yonelinas, 2002); however, fMRI and ERP/F findings seemed to be unconnected. We hypothesised that alpha rhythms would track the temporal and spatial signatures of recollection, providing a connecting link between these two apparently disparate lines of research.

Much of the research on recollection has been conducted using subjective ratings. In contrast, a strong point of our paradigm (*Figure 12*) was that it enabled to derive objective measures of item (old/new) and associative memory (recollection). Using this paradigm, we demonstrated that alpha desynchronization systematically tracks item and associative memory. Taking advantage of the excellent temporal resolution of MEG signals, we demonstrated that alpha desynchronization for associative memory (800ms) unfolded few milliseconds after item memory. This finding was highly congruent with previous late parietal ERP/Fs (Herron, 2007) components and, strikingly, with iEEG alpha power results in the human hippocampus (Staresina et al., 2016). The subsequent source-space reconstruction, not only pinpointed the contribution of the hippocampus but also of a set of regions highly congruent with the fMRI 'core recollection network' (*Figure 15*). Altogether, our data demonstrated that alpha desynchronization tracks recollection across time and space, suggesting that this brain rhythm may play a functional role in retrieval processes.

In *Chapter 2*, we revisited several of the retrieval neurocognitive models and current views on the function of alpha rhythms. Our results suggest an interesting link between some of these models and current proposals about the meaning of alpha rhythms on episodic memory. Source reconstruction revealed a remarkable engagement of the posterior parietal cortex, which agrees with the views of this region as an episodic buffer (Baddeley, 2000; Rugg & Vilberg, 2013). In parallel, a recent framework

points that alpha desynchronization in neocortical areas reflects the representation of information (Hanslmayr et al., 2012; Hanslmayr et al., 2016). Although our data is substantially congruent with these models and may provide experimental evidence for their future developments, we noted that alpha desynchronization parietal sources were more superior than what has been previously reported for recollection (Nelson, McDermott, Wig, Schlaggar, & Petersen, 2013). We thus founded our interpretation in the agreement with previous ERP (Vilberg et al., 2006; Wilding, 2000) and fMRI similar findings (Hayama et al., 2012; Thakral et al., 2017), but we do not rule out the possible implication of attentional processes (*see Chapter 2*) similar to Attention-to-Memory (AtoM) proposals (Ciaramelli et al., 2010). Taking into account the functional segregation of the parietal cortex (Nelson et al., 2010), future research is needed to identify the different roles of alpha rhythms across this regions. E.g., may alpha rhythms play a double role during recollection, being the superior parietal power decrease linked to attention and the inferior linked to information representation/maintenance?

Building on previous studies linking alpha power decreases and BOLD signal (Laufs et al., 2006, 2003), our hypothesis was mainly related to the alpha band. However, based on previous iEEG (Burke et al., 2014) and MEG (Osipova et al., 2006) studies, and the central role of theta rhythms on stimulus coding and LTP (Düzel et al., 2010; Kahana, Seelig, & Madsen, 2001), one would ask why we did not find any result in the theta band. The reasons for this result are not entirely understood. First, we note that our experimental paradigm differs from the abovementioned studies which used recognition memory (old/new) and free recall. In the second place, the latencies of the theta band effects tend to be earlier (300ms) than the ones presented here, so different processes may be involved. Strikingly, when a similar paradigm has been used (Staresina et al., 2016), coinciding hippocampal alpha desynchronization has been found at late latencies (800ms). Therefore, it is possible that both theta and alpha rhythms play a role during retrieval and may recruit different functional networks that are differentially captured by these particular paradigms.

Interesting venues may have been opened, for example, a causal relationship between the hippocampus and the left parietal cortex during associative memory was demonstrated using resting-state fMRI

functional connectivity and repetitive Transcranial Magnetic Stimulation (rTMS). Wang et al. (Wang et al., 2014) identified the individualised left lateral parietal location with highest resting-state FC with the hippocampus and applied rTMS. The stimulation of the lateral parietal cortex not only improved associative memory performance but also induced connectivity changes for a number of regions within this hippocampal-neocortical network. Our results indicate that alpha rhythms may be the oscillatory mechanism through which PPC and hippocampus dialogue to support associative memory processes. Inspired by rTMS studies, a direct application of our results would be the interruption of recollection guided by alpha temporal and spatial dynamics.

Here, we identified the oscillatory mechanism that supports a well-known process in psychology: recollection, opening the possibility to unify the body of knowledge accumulated during the last decades. Recollection is at the core of human experience and, for example, it is impaired in Alzheimer disease and its prodromal stages (Millar et al., 2017). Moreover, beta-amyloid depositions –a possible biomarker of the disease– are localised over parietal and MTL regions (Rodrigue, Kennedy, & Park, 2009), so, before addressing more subtle expressions of online reactivation, a good understanding of recollection is needed.

Some potential weak points need to be considered throughout the experimental work of this thesis. First, the sample size (N = 15) and the specific stimuli (words) might limit the generalizability of the results. Future studies should consider increase the number of participants and use different stimuli (scenes, videoclips…). Second, as already indicated on the discussion of each experimental study, careful consideration should be given to the findings of deep sources (i.e., hippocampus). Although an increasing body of evidence is demonstrating the reliability of MEG hippocampal signals (Pu et al., 2018), we lacked of individual MRIs to conduct a more accurate source-space reconstruction. Future studies may consider using individual MRIs, optimising the source reconstruction for hippocampal sources with a procedure similar to the one followed by Backus, Schoffelen, Szebényi, Hanslmayr, & Doeller (2016). Third, at the stage of encoding it would have been interesting to study subsequent memory effects and link them to offline reactivation and recollection; however, the limited number of misses in the deep condition

made challenging to address this question. A future solution would be increasing the difficulty of the retrieval task to yield a good amount of misses.

Both studies involved oscillatory activity in the alpha band in one way or another. The choice of this band for the frequency-tagging manipulation was merely made to maximise the probability of finding reactivation during offline periods. We selected the frequency band that has previously showed robust flicker effects (Keitel et al., 2014) and higher reliability on resting-state (Martín-Buro, Garcés, & Maestú, 2015). However, from the theoretical perspective, some interesting questions arises. For example, did we find reactivation because alpha oscillations are engaged on consolidation *per se*? Also, our data is far from solving the question of whether the flicker effect emerges as a result of the superposition of a series of ERPs (Capilla et al., 2011) or as result of entraining an oscillation (Thut et al., 2011). But it is intriguing that we found a significant power increase in the absence of an event, and therefore, in the absence of an evoked response. What is clear is that alpha oscillations play a crucial role in coordinating our cognitive processes and much research is needed to unravel its different contributions.

Despite the abovementioned limitations and remaining questions, this thesis provides considerable progress that can be summarised in two points. (i) Methodologically, it presents a novel implementation of oscillatory entrainment and a variety of analyses of the MEG data: MVPA, power and time-frequency decomposition both in sensor and source space. (ii) Conceptually, we linked our findings to well-founded cognitive and neurobiological models. Furthermore, this thesis addressed classical questions in psychology, such as deep/shallow encoding and recollection; as well as novel challenges like offline reactivation. We also studied the evolution of a memory trace across its lifespan (encoding, consolidation and retrieval) providing a comprehensive study of determinant aspects of human memory.

Besides the experimental work, this thesis tried to present an up-to-date view of how human memory works and what questions remain unsolved. Without an adequate analysis of offline and online reactivation, we undervalue its impact and waste the opportunity to exploit it to improve learning strategies, relieve the recurrence of traumatic memories or set targets of neuropsychological rehabilitation.

2. Conclusions

Human memory is the result of a highly dynamic process in which reactivation seems to play a critical role. Although neuroimaging techniques have pinpointed the critical regions of reactivation phenomena, these results remain unconnected from the neurophysiological models and invasive recordings in humans and animals. Whole-head electrophysiological techniques such as MEG may arise as the middle ground to complete the picture of how the brain system coordinates behaviour. This doctoral thesis contributes to do so by describing the relationship between oscillations and behaviour in two critical moments of episodic memory processing: consolidation and retrieval. Notably, we demonstrated that oscillations enable to track cognitive and neural mechanisms of episodic memory from offline resting periods to conscious and vivid recollection.

First, our data expand our current understanding of mPFC-MTL circuits during awake consolidation. Although the role of the MTL during consolidation was already well-established we demonstrated: (i) that not only spatial (Staresina et al., 2013) but also oscillatory reactivation can found on MTL regions; (ii) MTL with mPFC reactivation predicts memory performance , suggesting a functional role during consolidation; (iii) mPFC offline reactivation is not restricted to recent memories. These findings are in good agreement with prevailing models, but also challenge the proposals that link the role of mPFC to exclusively remote memories (Tompary et al., 2017).

Second, in an attempt to unify fMRI and ERP/Fs research, we describe a putative mechanism to support the traditional recollection findings. Explicitly, our data unveil that alpha desynchronization constitutes a fundamental oscillatory mechanism that may underlie the fMRI recollection network and posterior parietal ERP components. Therefore, using a single technique, we described how memories unfold over time and space. Intriguingly, this is the first time that alpha desynchronization is described during recollection since previous reports found effects on the theta and the gamma band (Osipova et al., 2006). Worthy of note is that our data highly overlap with iEEG evidence in the human hippocampus and may provide evidence for recent proposals

(Hanslmayr et al., 2016) on the role of oscillations in episodic memory. In the light of these proposals, alpha desynchronization may be reflecting the representation of information during peri-retrieval operations, but additional experiments are required.

To conclude, our results demonstrated that MEG oscillatory patterns in the alpha band can track when and where memories are reactivated from consolidation to retrieval, providing robust evidence to evaluate prevailing theories and models on episodic memory.

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