UNIVERSITAT DE BARCELONA

Exploring autobiographical memories: from neurocognitive mechanisms to real-life experience

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List of abbreviations

AM	Autobiographical memory
BA	Brodmann area
BOLD	Blood Oxygen Level Dependent
CLS	Complementary learning systems
EC	Entorhinal cortex
EEG	Electroencephalography
ERP	Event-Related Potential
fMRI	functional Magnetic Resonance Imaging
FOV	Field of view
FU	Follow-up (from six months to one year after the encoding)
HSAM	Highly superior autobiographical memory
iEEG	intracranial electroencephalography
IT	Inversion time
LEC	Lateral entorhinal cortex
LPE	Late parietal effect
LTM	Long-Term Memory
MEG	Magnetoencephalography
MFG	Middle Frontal Gyrus
MTT	Multiple trace theory
MVPA	Multi-voxel pattern analysis
PFC	Prefrontal Cortex
PMN	Parietal mode network
PRC	Perirhinal cortex
RT	Reaction Time
SCM	Standard consolidation model
SMS	Self-memory system
T1	Test one (one week after the encoding)
T2	Test two (two weeks after the encoding)
TE	Echo Time
TLE	Temporal lobe epilepsy
TR	Repetition time

Abstract

Our daily life event experiences fall into two general classifications: those that are remembered and those that are not. The act of remembering involves a perfect gearing of neurocognitive operations that begin with the encoding of information and conclude with the retrieval of a complete memory. The success or failure of any of these operations will determine the fate of a memory.

Capturing memory processes and their dysfunction in real-life situations is technically and methodologically challenging. Therefore, much basic and clinical memory research uses highly controlled materials and tasks, recorded by pen and paper or on a computer in a laboratory setting. While such an approach is extremely powerful in allowing good experimental control and straight-forward analysis of many parameters, such artificial paradigms fail to provide valid conclusions on function and impairment in naturalistic real-life situations. In this thesis, we explored some of the factors that can influence the encoding and retrieval of memories with the aim of developing novel approaches that enhance ecological validity.

Relative to the process of encoding, in Study 1, we studied how the integration of new information into long-term memory takes place when novel experiences overlap with existing structures of memory networks. In particular, we focused on understanding whether the nature of these overlapping representations, either at episodic or semantic level, could affect the process of integration into a relational memory network. Our neurophysiological results supported the notion that different neural responses and mechanisms subserved memory integration processes and they differed as a function of the underlying relational network properties. Given its clinical relevance, we also examined the role of the hippocampus in inferential learning by exploring the generalization ability of a group of TLE patients with specific lesions at the MTL structures. Our behavioural results showed that the hippocampus is a key structure that support mnemonic generalization.

In study 2, we propose a novel naturalistic approach that share the overall aim of bridging the gap between the highly controlled yet artificial laboratory studies and the more ecologically-valid processes that occur in everyday life. In this study, we developed a new experimental approach that allowed us to extract individual experiences from real-life episodic routine and used them as cues by using a convolution network-based algorithm (SR-clustering). With these individual cues we also explored how the pass of time impacted on the retrieval of these event episodes assessing their recollection one week, two weeks and 6 to 12 months after the encoding period. Additionally,

participants also enrolled into a separate study that require them to encode and retrieve lab-based pictures, not related with their personal experiences, to delineate the feasible differences between retrieval processes cued by real-life autobiographical vs lab-based event experiences. Our behavioural results suggested that picture cues were effective in eliciting the retrieval of Autobiographical Memories (AMs). Furthermore, from our neurophysiological results we observed that these 'cues' clearly triggered a solid differential response when compared to pictures depicting other's past.

In study 3, we used functional Magnetic Resonance Imaging (fMRI) to investigate the brain regions engaged during the retrieval of AMs for single event episodes cued by pictures recorded by healthy adults through a wearable camera for 4 consecutive days. The findings of this study corroborate that the use of real-life picture cues elicit the activation of a core AM brain network of regions that can be observed even at the individual level.

Altogether, this thesis provides novel insights into how encoding and retrieval processes unfolded and contributed to exciting and debated topics about the cognitive and neural mechanisms that support autobiographical memories. I hope that the findings and the thoughts contained in this thesis would be useful to start novel research initiatives that improve our understanding of the mechanisms that govern human memory.

Resumen

Nuestras vivencias del día a día se pueden clasificar entre las que recordaremos y las que no. El acto de recordar implica un perfecto engranaje de operaciones neurocognitivas que comienzan con la codificación de una información y concluyen con la recuperación completa de una memoria. El éxito o el fracaso de alguna de estas operaciones determinará el destino de esa memoria.

Ser capaces de capturar estos procesos y sus errores en situaciones de la vida real es metodológica y técnicamente un reto. Por lo tanto, mucha de la investigación básica y clínica en el campo de la memoria utiliza estímulos y tareas en condiciones controladas, administradas en lápiz y papel o en un ordenador en un entorno de laboratorio. Aunque este enfoque cuenta con puntos fuertes en el control experimental y en el análisis directo de muchos parámetros, estos paradigmas artificiales no son capaces de ofrecer conclusiones válidas que expliquen la función y el deterioro en la vida real. En esta tesis, hemos explorado algunos de los factores que pueden influenciar la codificación y recuperación de la memoria con el esfuerzo de desarrollar nuevos enfoques que aumenten la validez ecológica.

Referente al proceso de codificación, en el estudio 1, estudiamos cómo tiene lugar la integración de una nueva información en la memoria a largo plazo cuando se solapa con estructuras de redes de memoria ya existentes. En particular, nos centramos en entender si la naturaleza de estas representaciones solapadas, tanto a nivel episódico como semántico, pueden afectar al proceso de integración en una red de memoria relacional. Nuestros resultados neurofisiológicos apoyan la idea de que diferentes respuestas y mecanismos neuronales favorecen los procesos de integración y que se diferencian en función de las propiedades relacionales de la red. Dada su relevancia clínica, examinamos también el papel que el hipocampo tiene en el aprendizaje inferencial mediante la exploración de la habilidad para generalizar de un grupo de pacientes con epilepsia en el lóbulo temporal y con lesiones específicas en el lóbulo temporal medial. Nuestros resultados conductuales mostraron que el hipocampo es una de las estructuras principales que sustenta la generalización.

En el estudio 2, proponemos un enfoque nuevo que abarca el objetivo general de establecer puentes entre estudios artificiales que estén altamente controlados a nivel experimental con procesos más ecológicos que ocurren en el día a día. En este estudio, desarrollamos un protocolo que nos permitió extraer experiencias individuales de las rutinas diarias y usarlas como pistas de recuperación aplicando un algoritmo (SR-Clustering). Con estas pistas de recuperación tomadas individualmente, exploramos también cómo el paso del tiempo impacta en la recuperación de los

eventos episódicos al evaluar el recuerdo a una semana, dos semanas y de 6 a 12 meses del periodo de codificación. Además, los participantes también formaron parte de otro estudio donde se les requería que codificaran y recuperaran imágenes artificiales creadas en el laboratorio, y que no tenían ninguna relación con sus experiencias personales, para delimitar posibles diferencias entre los procesos de recuperación generados a partir de experiencias autobiográficas comparadas con las de laboratorio. Nuestros resultados conductuales sugieren que las fotografías utilizadas fueron efectivas ya que provocaron la recuperación de memorias autobiográficas. Además, nuestros resultados neurofisiológicos mostraron que estas pistas de recuperación eran capaces de producir una clara y sólida respuesta diferente a la producida por fotografías que mostraban el pasado de otras personas.

En el estudio 3, usamos resonancia magnética funcional (fMRI) para investigar las regiones del cerebro que se activan al recuperar memorias autobiográficas usando fotografías tomadas por adultos sanos con una cámara portátil durante 4 días consecutivos. Los hallazgos de este estudio corroboran que el uso de imágenes reales provoca la activación de una red central de regiones relacionadas con la memoria autobiográfica que pueden observarse a nivel individual.

En resumen, esta tesis ofrece nuevas ideas acerca de cómo se desenvuelven los procesos de codificación y recuperación de la memoria, y contribuye a fomentar el debate existente entre los mecanismos cognitivos y neuronales que sostienen la memoria autobiográfica. Espero que los hallazgos y pensamientos que contiene esta tesis puedan ser útiles para fomentar nuevas investigaciones y mejorar el entendimiento de los mecanismos que gobiernan la memoria humana.

Chapter 1

Introduction

Chapter 1: Introduction

What is autobiographical memory?

When I look back to the beginning of this PhD, I picture myself seated in front of my supervisor talking about research possibilities in the university canteen. I can recall the context, the situation, the time of the day, my emotions and even how long it took me to get to Bellvitge University campus for the first time. When we think of what autobiographical memory is, a combination of different types of knowledge and personal and important representations come to mind.

Autobiographical memory can be thus defined by the memory representations of one's personal history that integrate self-related knowledge with experienced events (Conway, 2001; Levine et al., 2004; Rubin, 2006), constructed by a variety of factors such as emotions, self-schemas, goals, among others. Autobiographical memory helps us define who we are, allowing for future planning in which a continuous self operates (Conway & Williams, 2008). The study of autobiographical memories has increased over the last 2 decades; however, these studies have generally used materials that mimic real-life events, though they have been created and controlled by the experimenter in the laboratory (lab-based studies).

These lab-based events were studied under the assumption that a memory system termed Episodic memory was in charge of dealing with memories that related to personal event-experiences. These memories were conceptually and operationally different from our memory representations regarding general facts, linguistic concepts, the world and ourselves (Endel Tulving, 1983). Thus, the primary role of the episodic memory system is to facilitate the conscious recollection of these 'events' in the spatiotemporal context in which they occurred. Although nowadays it is well accepted that the episodic memory system is dissociated from other kinds of memory systems (semantic memory), the nature of its neural manifestations (Cabeza & Moscovitch, 2013; Craik & Lockhart, 1972; Endel Tulving, 1983) raises the concern as to whether this view remains too simplistic.

In addition, it has been assumed that the neural and cognitive processes that underlie the encoding and retrieval of episodic memories could be generalized to those supporting autobiographical memories, making both concepts interchangeable (Kopelman & Kapur, 2001).

However, some have questioned this assumption (Conway, 2001; Levine et al., 2004; Wheeler, Stuss, & Tulving, 1997) arguing about important differences between how they interact as a function of lifetime period or the underlying representational nature embedded in their memory trace (more sensory detailed in episodic memory in contrast to more abstract representations for autobiographical memory).

Throughout this thesis, we explore the cognitive and neural mechanisms that operate in our daily-life experiences when encoding (see **section 1.1**) and retrieving autobiographical stimuli (see **section 1.2**).

1.1 Encoding

The events experienced in the course of our lifetime fall into two general classifications: those we remember and those we do not. Some events are remembered in the long-term, while others are forgotten, or even go unnoticed. Human memory studies have intensified their efforts to identify the cognitive operations that support the two principle processes that determine the fate of a memory: Encoding and retrieval. The first section is focused on the underlying operations of encoding, which refers to the process by which we transform external input information into an internal mental representation.

1.1.1 Theoretical frameworks

Since the pioneering studies of Bartlett (Bartlett, 1932) and Piaget (Piaget, 1960) we know that the encoding of new information is strongly influenced by the schema or the prior knowledge structures that have been acquired during past experiences. *Schema* refers to knowledge organized into an elaborate network of abstract mental structures, which represent one's understanding of the world (Bartlett, 1932). Several studies consider a schema to be the abstract 'gist' of knowledge derived by the extraction of regularities and the loss of the more peculiar aspects of each event. Further studies have shown that having a pre-existing schema when learning, facilitates memory consolidation allowing new information to be rapidly assimilated (Tse et al., 2007, 2011). Schemas represent relationships among elements commonly associated with certain types of situations, despite not been experienced together (e.g., a restaurant schema). This property serves to guide behaviour by providing a set of expectations for a given experience that may also support inferential decisions and guide how newly experienced events are encoded into memory (Schlichting & Preston, 2017).

The idea that stored structures of knowledge (i.e., schemas) interact with the encoding of new experiences is central in other influential theoretical frameworks. For example, the *Cognitive Map Theory* (Tolman, 1948) proposed that animals build an internal representation (a cognitive map) of their environment, and having this map allows the animal to navigate along paths, take shortcuts and remember the location of their nest or food source (Tolman, 1948). These actions, even occurring in spatial layouts that are completely new, are possible because of the nature of the internal representations (the representational scheme) constructed by the hippocampus. This representational scheme allows the integration across overlapping routes and the coding of the overall spatial layout of the environment, as it also occurs with information in the schema theory, leading to new inferences and generalization (Wu & Foster, 2014).

Other modern memory theories such as the *Relational Memory Theory* (Eichenbaum & Cohen, 2014; Eichenbaum et al., 1999; Konkel & Cohen, 2009) emphasized the nature of the hippocampal processes and its representations, including its role in binding together co-occurring elements of experience into a compositional representation or permitting the flexible reactivation of these representations in response to a wide variety of task demands. These ideas are also of great influence in the current views of how new memories are integrated within existing schemas and how these existing schemas are modified during memory consolidation (Preston & Eichenbaum, 2013; Van Kesteren et al., 2012).

1.1.2 How is information processed, organized and represented into a memory network?

Considering the functional anatomy of the brain system that supports memory for everyday events provides preliminary insights into how the brain encodes, organizes, and retrieves memories. Multiple sensory pathways initially process the information regarding the identity of perceptual objects and events, converging into multimodal cortical 'association' areas. These pathways refer to the stream of information flow for 'what' will be remembered. Another stream of pathways involving different areas of the cerebral cortex is in charge of processing 'where' in space we remember an object or event. Information processed from these different streams is then sent to the Medial temporal Lobe (MTL). More specifically, the perirhinal and lateral entorhinal cortex are thought to signal the degree of familiarity within a given object stimuli, and the parahippocampal and the medial entorhinal cortex in the processing of spatial contexts in which mnemonic events take place (see **Figure 4**). Within the MTL, all the information converges at the level of the hippocampus, which forms cohesive memories of individual events within the context in which they occurred (Preston & Eichenbaum, 2013).

Hippocampus outputs return to the cortical areas from where inputs arose. These feedback pathways allow the hippocampus to support the retrieval of information about 'what' occurred based on a cue about 'where' an event occurred, and viceversa. As a consequence, hippocampal processing supports the retrieval of detailed memories that constitute strong recollective experiences in humans (Eichenbaum, Yonelinas, & Ranganath, 2007).

Thus, critical to understanding how memory organizes information during encoding requires understanding which cognitive processes and neural mechanisms are sub-served in the hippocampus upon the initial experience of an event. The existing literature has shown that the hippocampus seems to mediate the process of integrating novel information into existing memory networks on the basis of three main non-mutually exclusive processes:

1) *Pattern separation/completion.* Considering that encoded information is not always completely new and often overlaps with previously acquired information, a process by which new encoding does not overwrite previous memories avoiding catastrophic forgetting is needed. Computational models emphasize two core mechanisms: pattern separation and pattern completion (Rolls, 2013). *Pattern separation* refers to the orthogonal coding of memories for overlapping events creating distinct, non-interfering representations of the information. *Pattern completion* refers to the reinstatement of previously encoded memories from a partial input, allowing the integration with the current experience.

2) *Binding of associative representations*. Retrieval-mediated learning is hypothesized to consist of a two-stage process that involves the reactivation of existing memories cued by overlapping events and the binding mechanisms that encode the relationships among past experience and current events (Zeithamova, Dominick, & Preston, 2012). Although isolating reactivation and binding processes remains a challenge in these kinds of studies, animal studies have demonstrated that hippocampal neurons develop generalized firing patterns that respond to similar locations in overlapping environments (Singer et al., 2010) suggesting that these hippocampal neurons build up representations that bind different experiences together by coding the similarities between events. By representing these similarities, hippocampal codes could capture regularities across experiences and act as 'nodes' linking behavioural episodes (Eichenbaum et al., 1999; Schlichting & Preston, 2017). Computational models of hippocampal function have highlighted the role of the Cornu ammonis field$_3$ (CA$_3$) neurons in the formation of relational networks (Wallenstein, Eichenbaum, & Hasselmo, 1998). These models proposed that these neurons develop 'context fields' during learning that bind together elements within a single

event and respond preferentially to temporary contiguous stimuli or events. These findings suggested that CA_3 binding processes are critical to the formation of an integrated memory.

3. *Memory integration*. Neuroimaging studies have shown that memory integration occurs during new learning (Shohamy & Wagner, 2008; Zeithamova & Preston, 2010). For example, some studies (Richter, Chanales, & Kuhl, 2016) have found that memory integration requires a processing state that is qualitatively different from encoding or retrieval and does not lie in between them. Pioneering research in healthy humans and rats (Bunsey & Elchenbaum, 1996; DeVito et al., 2010; Iordanova, Killcross, & Honey, 2007; Schlichting & Preston, 2017) has highlighted that the hippocampus is central, but by no means unique, in organizing and combining memories into mnemonic networks and that the medial prefrontal cortex (mPFC) is crucial for these processes too. Moreover, activity patterns in mPFC were more diagnostic of an integration state than hippocampus patterns, indicating that the mPFC, and in particular the ventromedial PFC (vmPFC), is essential for the integration of information and a fundamental part of the connections between cortical and subcortical networks that support episodic memories. vmPFC engagement could be related to the ability to successfully organize and infer relationships between overlapping events (Zeithamova et al., 2012). However, even though the vmPFC can play an important role in the integration of memories, evidence has pointed out that interactions between hippocampal-PFC are the ones that support this process and also underlie the initial formation of relational memory networks enabling subsequent inference via pattern completion and novelty detection. See **Figure 1**.

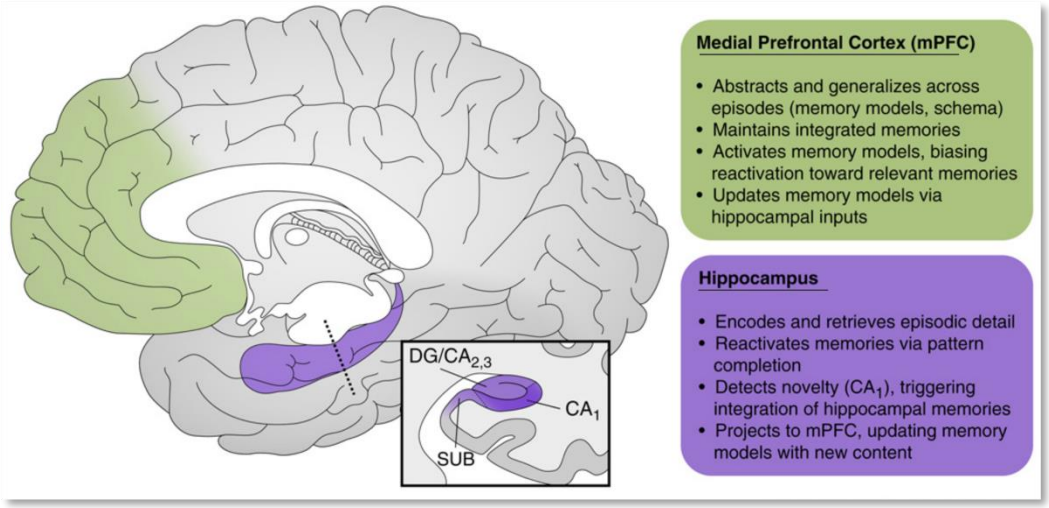


Figure 1. Suggested roles of the human hippocampus and mPFC in memory integration. Locations and hypothesized function of these regions: Purple, hippocampus, green, medial prefrontal cortex. Cross-section of the hippocampus (purple) highlighting area CA_1 (dark purple portion). Hippocampal subfields are indicated with thin dashed lines. CA_1, Cornu ammonis field $_1$, $DG/CA_{2,3}$ dentate gyrus and Cornu ammonis fields 2 and 3, SUB, subiculum. Adapted from Schlichting and Preston, 2015.

At the representational level and related to how the brain organizes the acquired information mnemonic information is arranged in the brain via a network of interconnected representations (Eichenbaum & Cohen, 2001). The links between this network arise from the overlap between independent episodes, and individual hippocampal neurons are able to develop representations that code for these similarities (McKenzie et al., 2013). The points of overlap would be represented as a hub or nodes in that network. Those nodal representations would contain information such as people, objects, landmarks, locations and perhaps even actions (Milivojevic & Doeller, 2013). However, how the hippocampus represents this information at the neural level is a question that is still being debated.

Figure 2 depicts three different hypothetical scenarios of how the hippocampus might associate and represent overlapping information in a memory network (from Zeithamova, Schlichting, & Preston, 2012).

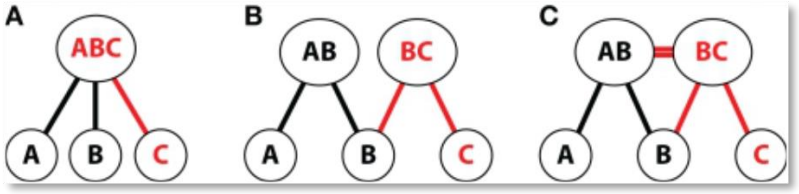


Figure 2. Schema depiction of alternative accounts of hippocampal representation in an associative inference task. Adapted from Zeithamova et al., 2012.

(A) Shows a hypothesized structure of a single integrated representation for overlapping events. New overlapping events (C) are encoded into an existing, reactivated memory (A) to form a single representation for the two related associations. This could be an example of how information is integrated and represented by the cognitive map theory (O'keefe & Nadel, 1979; Tolman, 1948) in which newly learned individual events (i.e., recently traveled routes) are combined with previous knowledge for the creation of an integrated map of the environment, including information about paths not previously traveled.

(B) Other computational perspectives (Kumaran & McClelland, 2012; Shohamy & Wagner, 2008) propose a different representation for the hippocampus in which pattern separation processes maintain distinct individual experiences. Furthermore, the connections between them and the shared element event (B) are also maintained, allowing inference across experiences.

(C) Relational memory theory (Cohen and Eichenbaum, 1993) represents an alternative view that combines A and B. This theory proposes that the hippocampus maintains representations of individual events but also maintains the encoding relationships between separate experiences (Eichenbaum et al., 1999).

1.1.3 How are memory networks organized when information requires different levels of representation?

Mnemonic concepts are thought to be represented at multiple hierarchical levels (Milivojevic & Doeller, 2013). The representations of individual events would appear at the lowest level in a mnemonic hierarchy (e.g., reading this thesis). On the next level in a mnemonic hierarchy, at a 'medium-scale' module, would be the representation of conceptually narrower mnemonic item (e.g. reading thesis in general). These medium-scale modules would represent information which could be defined as individual mnemonic items (specific individuals, objects, locations, landmarks or actions) abstracted from individual episodes from which they are acquired and would form the nodes of the mnemonic network. The next hierarchical level would represent information in 'coarse-scale' with reduced detail of those representations, losing the differences between them.

Experimental evidence provides support to the notion that different levels of representation coexist and that they may be organized along the hippocampal longitudinal axis. Human neuroimaging research has shown that detailed forms of memory are mapped onto the posterior hippocampus and posterior MTL structures, while more abstract forms are mapped onto the anterior MTL structures (Poppenk et al., 2013; Ranganath & Ritchey, 2012). Thus, when several mnemonic concepts co-occur, their neural patterns coactivate, simultaneously, strengthening the connections between the cells that code for those concepts. Commonly co-occurring mnemonic concepts might result, at some point, in the formation of a new mnemonic concept that would represent both at a coarser mnemonic resolution.

New concepts are likely to be integrated into pre-existing networks when there is an overlap between new and previously encoded events. It has been shown that the cerebral structures comprise several areas of the MTL that are interconnected and follow a hierarchical structure in their processing. Neurons in the MTL presented different levels of selectivity to the stimuli, with the highest selectivity of neurons in the hippocampus to the lowest selectivity in the parahippocampal cortex. This hierarchical processing at the MTL suggests that there is an increase of abstract representation along the MTL that leads to the encoding of the meaningful stimulus. **Figure 3** provides a schematic illustration of how memory representations may be coded throughout the MTL areas according to Quiroga, 2012. The processing of the information activates projections from the parahippocampal and perirhinal cortices that receive direct inputs from cortical areas that then arrive to the entorhinal cortex, which in turn projects onto the hippocampus, at the top of the MTL hierarchical structure. The amygdala has direct connections to the other MTL areas and to sensory cortex. Although the conceptual representation culminates in the hippocampus, this representation is also present in other MTL areas to a different degree.

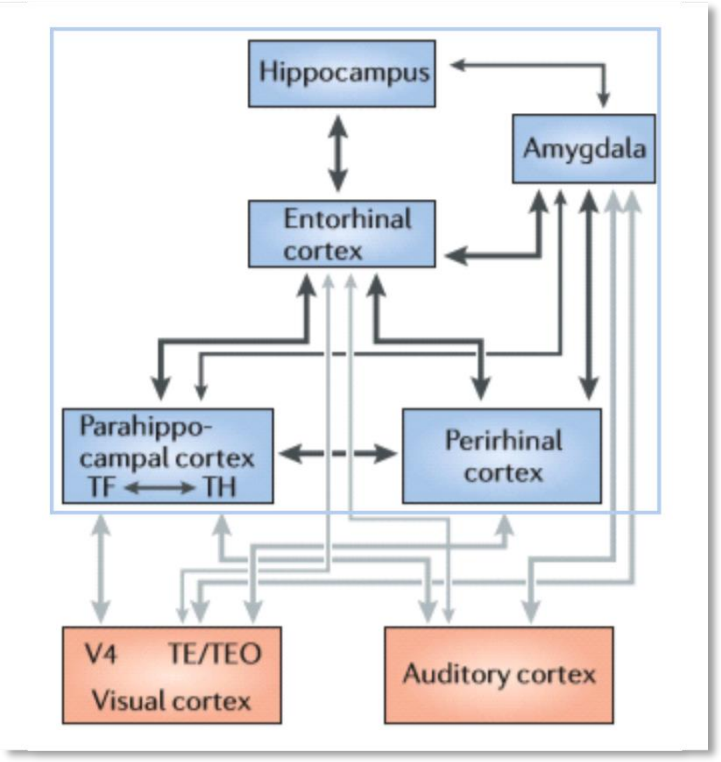


Figure 3. Hierarchical processing in the human medial temporal lobe. The connectivity between MTL with the visual and auditory cortex are marked with black and grey arrows, respectively. TE, temporal area, TEO, temporal occipital area. Adapted from Quiroga, 2012.

The MTL and cortical areas also contribute to the construction of these conceptual representations. For instance, participating in relating concepts such as linking somebody's name with a face. MTL neurons fire when exposed to pictures of people as well as their spoken and written names. Therefore, viewing a person's picture as a stimulus would activate direct projections to cortical areas that in turn, evoke responses in MTL neurons that bundle different concepts into a single concept. These associations may be later stored in the cortex and could be reactivated through pattern completion mechanism.

The MTL, therefore, appears to be crucial in creating links between different, yet overlapping, event representations. Indeed, studies have shown that damage to the hippocampus is sufficient to create a memory integration deficit between overlapping events, even when the memory of individual associations is relatively well preserved (Pajkert et al., 2017). For instance, patients with mild hippocampal atrophy showed a preserved ability to learn simple stimulus associations but showed a deficit on how associations are learned (Myers et al., 2003). Specifically, hippocampal damage may cause patients to learn the initial associations between pairs of items in a way that made them less able to transfer and generalize to novel contexts, thereby impeding the ability to make associative inferences.

1.1.4 Hippocampal - Prefrontal Cortex interactions during memory formation

As pointed out in the previous sections during encoding, the hippocampus and the mPFC are key structures leading our ability to combine related memories. The result of the interaction between the two neural regions may determine inferential learning during the encoding of overlapping memories (Richter et al., 2016) and whether we would remember them long term (Ranganath et al., 2005). However, each of these structures offer distinct contributions as to how different memories can ultimately become integrated.

The hippocampus has been found to be important in establishing associations between item objects within an event and how they are bound together in the mnemonic network. For example, fMRI studies have shown that the activation of the hippocampus correlates to successful encoding of face-name (Sperling et al., 2003), face-house (Henke et al., 1997) and word-word associations (Henke et al., 1999). In addition, the magnitude of the hippocampal activation is correlated with the number of associations bound into a single memory (Staresina & Davachi, 2008). The hippocampus has been also shown to be relevant for encoding specific stimuli within its spatial context (Davachi, 2006; Eichenbaum et al., 2007). Hippocampal neurons could also connect associations between distinct events that occurred in the same or different contexts (Ezzyat & Davachi, 2014), and also in those cases that they were encoded in different periods of time (Nielson et al., 2015).

The hippocampus also participates in more complex schematic organizations in which the links between the elements are beyond their simple association. For example, the hippocampus has been found to participate during a task that required the participants to take decisions based on input patterns structured around an abstract structure of relations between them (Kumaran et al., 2009). Besides, the hippocampus has been shown to participate in integrating different social episodes into a schematic organization mapping the social space (Tavares et al., 2015) (see also The importance of memory networks in real-life).

The PFC, on the other hand, is thought to contribute by exerting a top-down control of memory processing (Preston & Eichenbaum, 2013). Studies of patients with damage in the PFC have shown that they do not suffer severe impairments on episodic memory but show difficulties in memory tasks when the task involves interference or distraction conditions (Szczepanski & Knight, 2014; Shimamura et al. 1995). Patients with PFC lesions also show intrusions of irrelevant memories in studies of attention to specific cues, thereby indicating that the PFC may be crucial for learning to switch between memory strategies in various tasks (Rich & Shapiro, 2007).

The mPFC may be the part of the PFC that helps deal with the conflict caused by the encoding of new inputs that overlap with existing information in memory by facilitating their assimilation into an update memory representation (Guise & Shapiro, 2017). The mPFC also seems to be crucial post learning during the initial stages of memory consolidation (Kitamura et al., 2017) and has extensive connections with a diverse set of sensory, limbic and subcortical structures (Cavada, 2000).

However, even though research have shown that these two mnemonic brain structures may support specific processes during the encoding of novel events, there is in fact strong evidence in rodents and humans that the mPFC and the hippocampus interact and are involved during the integration of new information into existing knowledge organizations (Milivojevic, Vicente-Grabovetsky, & Doeller, 2015; Tse et al., 2011). Anatomically, the hippocampus and the PFC are strongly connected by *direct* and *indirect* pathways (Preston & Eichenbaum, 2013). The first pathway is a monosynaptic projection from the CA1 of the ventral hippocampus to all layers of the mPFC and the orbital PFC. This projection provides the most immediate access to the PFC. The firing patterns of these ventral hippocampal neurons showed spatial and contextual coding concerning global information about the context of current events rather than detailed memories. Two other main indirect pathways that exist involve a single intermediary between the hippocampus and the PFC: one via thalamus and the other via cortical route. The thalamus pathway includes bidirectional connections through CA1, perirhinal cortex and entorhinal cortex. The cortical pathway includes connections between PFC through the perirhinal cortex and lateral entorhinal cortex, which in turn are connected to the hippocampus (Agster & Burwell, 2009). **Figure 4** illustrates some of the pathways that may connect the hippocampus with the prefrontal cortex.

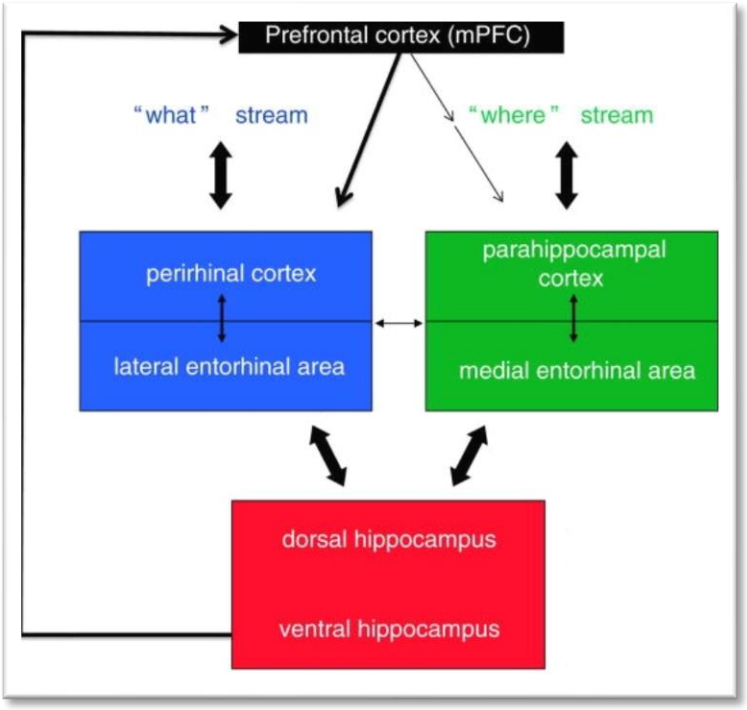


Figure 4. Pathways of information flow between the hippocampus and the Prefrontal cortex. Perceptual information about objects and events is initially processed in pathways for specific sensory modalities which project to multiple 'association' cortical areas (temporal, parietal and other cortical areas) composing the 'what' stream that lead to the blue box. Information about 'where' is processed in a separate cortical stream (including posterior parietal, retrosplenial and other cortical areas) that lead to the green box. These streams then converge in the hippocampus. Adapted from Preston & Eichenbaum, 2013.

Despite the evidence about the importance of the hippocampus and the PFC in memory integration, the specific neural mechanism by which this takes place is still an important topic of current research.

1.1.5 Theta oscillations during encoding

The studies aiming to identify how the hippocampus and the PFC regions are coordinated during memory formation highlighted the relevance of low-frequency oscillatory neural activity by which the two regions may be synchronized during memory formation. This neural oscillatory pattern appears at low frequencies in the range of 4-8Hz, at the so-called theta rhythm.

Animal studies typically involved correlating spiking activity in the mPFC with the local field potentials in the theta band of the dorsal hippocampus, revealing the relevant role of theta supporting spatial memory and navigation (Ekstrom et al., 2005; Jacobs et al., 2013). These studies have shown that these oscillations could be found at encoding when an animal explores its environment (Huxter, Burgess, & O'Keefe, 2003; O'Keefe & Recce, 1993), but also at retrieval

(see Hippocampal theta oscillations at retrieval) when the animal retrieves information about a previously explored layout (Foster & Wilson, 2007; Johnson & Redish, 2007).

Electrophysiology studies in humans have demonstrated that theta within the MTL (hippocampus and parahippocampal cortex) supports spatial navigation and that it correlated with travelled spatial distance within an event (Bush et al., 2017; Ekstrom et al., 2005; Herweg et al., 2018; Vass et al., 2016). These findings have provided evidence that MTL theta activity may reflect a code by which the brain constructs internal maps of the environment that may ultimately help establish specific associations between experienced contexts of our episodic memories (Eichenbaum, 2000; Herweg & Kahana, 2018; Squire & Zola-Morgan, 1991). The extent to which theta rhythm codes representational distances beyond the spatial-contextual level of representation remains unclear. However, a recent human study revealed that theta activity within the MTL may support both navigation and episodic memory search and that theta oscillations could also be correlated with representational distances of information (Solomon et al., 2019). In one of the studies included in this thesis (see Chapter 3), we explored how theta oscillations could help us to understand the organizational properties of how memories are stored. We also hypothesized that theta may in fact, signal a search process throughout representational space with different levels of semantic representation.

In the context of memory integration, it is widely accepted that the hippocampal-PFC coordination during encoding is supported by their long-range theta synchrony. The notion that the two structures oscillate at similar frequencies relies on the mechanistic principle by which oscillatory coupling underlies the exchange of information between distant regions in the brain (Fell & Axmacher, 2011). In fact, recent human studies studying magnetoencephalographic (Backus et al.,2016) and EEG (Sans-Dublanc et al., 2017) activity from the scalp, provided converging evidence that theta activity could support the successful integration of distinct memories that overlapped in content. The degree to which theta is involved in integrating distinct memories that overlap in different levels of representation and the extent to which this relay on the hippocampus is a question that we address in the current thesis (see Chapter 3).

1.1.6 The importance of memory networks in real-life

An important property of adaptive behaviour is the ability to rapidly differentiate what is new from what is familiar in our environment. When a stimulus is familiar, we may have the possibility to incorporate more information into our schemas or memory networks and update our knowledge about the world that is constantly changing.

Our day to day life demands access to our memories and the ability to employ this accessed information in a variety of situations, including novel circumstances. The ability to rapidly compare and contrast novel information with existing stored memories is a crucial property of our memory systems to foster flexible and adaptive behaviour as it supports inferences and generalization across experiences. The degree of mnemonic flexibility, provided by memory integration mechanisms, is also an important feature of memory because it has implications on other cognitive domains, bringing behavioural benefits such as inferring novel routes during spatial navigation, mapping social space, decision making, creativity and imagination (Schlichting & Preston, 2017). For example, in a recent study (Tavares et al., 2015) participants completed a role-playing task. During the task, characters moved across social space due to changes in power (competence, dominance, hierarchy, etc.) and affiliation (warmth, intimacy, trustworthiness, love, etc.). Researchers hypothesized that the hippocampus is able to construct an abstract geometric representation of social relationships during social interactions and tracks these relationships to represent our position in the social world. They found that hippocampal engagement was modulated by the position of the character in social space suggesting the formation of a cognitive map of social space from an egocentric view.

Memory integration is also considered to be a constructive process as it recombines prior memories with the goal of generating new ideas or recreating future scenarios (Schacter et al., 2012). Previous evidence has shown that the connectivity between the mPFC and the hippocampus is enhanced during the imagination of scenarios that would later be remembered (Martin et al., 2011). In another study (Barron, Dolan, & Behrens, 2013) participants needed to construct novel representations of novel foods from two familiar ingredients. They found that the neural representation of a novel reward was dependent on the representations of the related and previously experienced rewards (the ingredients) and that the construction of a novel experience depends on the hippocampus and the mPFC, which also constructs and valuates the items according to behavioural relevance.

All in all, memory integration could be considered the result of a number of neural mechanisms that favours the encoding of experiences in our daily life and further allows us to learn from the past and provide a means to project our selfs in the future.

1.2 Retrieval

The ability to retrieve information from the past into the present may stand as one of the most remarkable capacities of the cognitive system. It highlights our ability to mentally travel back in time and reproduce past experiences with a certain degree of detail. Like encoding, the process of retrieval is an essential process that determines the fate of a memory.

At the beginning of experimental research in memory, most studies were focused on understanding the cognitive underpinnings underlying encoding and forgetting. The general consensus at that time was that any decline in memory performance was the result of two possible scenarios: a failure because the information had not been learned or a failure because the information had been subsequently forgotten. In 1966, Tulving and Pearlstone (Endel Tulving & Pearlstone, 1966) reported a finding that would change the direction of memory research: they revealed memory failure could reflect a problem in retrieval, thereby suggesting there should be a distinction in the notion that memories can be available, accessible or the two of them. Tulving stated that some forms of memory failure reflect a lack of availability of information (i.e., permanent loss), whereas other forms of memory failure reflect temporary problems in accessibility. One example of the difficulty in the accessibility of memories encountered in our everyday life is the so-called 'tip of the tongue' phenomenon, in which people are sure they know some fact but cannot recall it explicitly. Eventually, this information comes to mind reflecting that the availability of cues at retrieval could be essential for remembering.

In subsequent experiments (Endel Tulving, 1983), Tulving also recognized an earlier work by German scientist Richard Semon (Semon, 1904), who was the first to introduce two concepts that became fundamental to the cognitive psychology of memory retrieval: 'Ecphory' and 'engram'. Ecphory was described as the unique interplay between cues and stored memory traces at retrieval, and engram referred to these memory traces as biological entities. According to Tulving, for remembering to occur, an appropriate retrieval cue must be present to initiate the process of retrieval (Tulving et al., 1983). Therefore, *retrieval* refers to the process initiated by a retrieval cue that leads to the emergence of a conscious and accessible representation of a specific past episode (Rugg, Johnson, & Uncapher, 2015).

A retrieval cue may take the form of an external event or might be generated internally. In experimental terms, retrieval cues could be tested under laboratory conditions with minimal and maximal cueing through free recall and recognition. Free recall (internal cue) is when the participant has minimal information to recall recently studied material. The opposite condition is recognition (external cue) in which the item to be remembered is shown, along with other items

not previously studied, and the participant is asked to identify the correct item. A moderate degree of prompting is cued recall (external cue), where the category of the information or part of the item is shown. The common finding across most experimental studies is that performance is generally higher in recognition compared to other forms of cueing, showing that retrieval cues (external or internal) have a strong influence on the retrieval of memories. The presence of these cues and how they are processed may determine how successful the retrieval is, highlighting the fact that these cues must be specific in order to be effective and that the retrieval of our experiences is cue dependent.

How can a simple cue trigger the retrieval of a "complete" memory?

1.2.1 Theoretical frameworks

The possibility to complete a full memory representation from the presence of a small part of it (i.e., cue) has been a focus of intense research during the past decades and motivated the emergence of influential computational models, psychological frameworks and neurobiological studies for many years, leading to several generally agreed conclusions.

Firstly, there is an interdependency between the encoding and the retrieval of episodic information. As postulated by the Transfer-Appropriate Processing (TAP) framework (Morris, Bransford, & Franks, 1977), memories are represented in terms of the cognitive operations engaged by an event. Therefore, the retrieval of an episodic memory involves the recapitulation of those operations engaged at the time of encoding. This idea was also found in other neurobiological-based models of episodic memory retrieval (Alvarez & Squire, 1994;Johnson, McDuff, Rugg, & Norman, 2009; McClelland, McNaughton, & O'Reilly, 1995; Norman & O'Reilly, 2003; Rolls, 2000; Rugg, Johnson, & Uncapher, 2015), framed by the *Complementary Learning System (CLS)* (McClelland et al., 1995). The CLS formulates the process of retrieval as an interplay between the cortex and the hippocampus. The retrieval of a recent event occurs if the pattern of cortical activity elicited by this event, when it was initially encoded, is reinstated in the hippocampus at the moment of retrieval. This happens because when we encode an event, apart from generating a pattern of cortical activity, the CA_3 region of the hippocampus creates a spared representation of that event. Critically, CA_3 is highly effective at *pattern completion* (Marr, 1971; Wallenstein et al., 1998) so, at retrieval, a cue that partially overlaps with the previously encoded information can be sufficient to activate the CA_3 hippocampal system that would reactivate, in turn, the original cortical pattern (see *Hippocampal indexing theory* below). Through this mechanism, anatomically different regions that were active during online processing of an event

will also be co-activated at the retrieval, preserving specific associations, relational processes (Eichenbaum et al., 2007) and making experiences unique compared to similar ones (Rugg et al., 2015).

One of the most influential applications of the CLS approach was in the domain of human recognition memory, in which recollection versus familiarity contributions have a controversial history. The debate focuses around the nature of familiarity and recollection-based recognition and whether they entail the same or independent processes. Some evidence claims that differences between them are only quantitative, and that they relay simply on a signal strength parameter (Squire, Wixted, & Clark, 2007) or confidence (Dunn, 2004). However, the dual-process model of recognition memory (Yonelinas, 2002) posits that recollection involves the explicit recall of the studied item (with the associated episodic context), and if it occurs, the participants could respond 'old' to an item with a high level of confidence. In contrast, familiarity is driven by a match between the stimulus and the stored memory items, that could be a graded, continuous memory signal unaccompanied by explicit context recall.

Another generally established idea in the research community is that the hippocampus has a pivotal role in the retrieval of memories as it acts as a hub connecting a host of multimodal regions and indexing the reinstatement of cortical patterns (Moscovitch etal., 2016). These principles are embraced by the influential *hippocampal indexing theory* (Teyler & DiScenna, 1986; Teyler & Rudy, 2007) that posits that the hippocampus was functionally designed and anatomically situated to capture information about neocortical activity. To accomplish this, the theory assumes that a particular episode is formed by individual features that activate patterns of the neocortical activity. This pattern of activity projects onto the hippocampus and, as a consequence, synapses in the hippocampus respond to these neocortical inputs and strengthen. During encoding, the outcome of this neocortical-hippocampus interaction is a hippocampal memory trace that results from the co-occurrence of patterns of activity in the neocortex. At retrieval, a subset of the original input pattern is received by the neocortex. The projections of these input patterns activate the neurons in the hippocampus representing the original experience (i.e., index). The activation of these representations projects back to the neocortex, which in turn conveys the indexing property of the hippocampus, and results in the activation of the pattern that represents the entire experience. Thus, the hippocampus itself does not contain the content of experience; it only provides an index to retrieve. The theory also speculates that, as a result of repeated activation of the index, the connections among the neocortical patterns might be gradually strengthened. Therefore, in principle, the retrieval of the memory might no longer have to go through the hippocampal index. **Figure 5** summarizes this process.

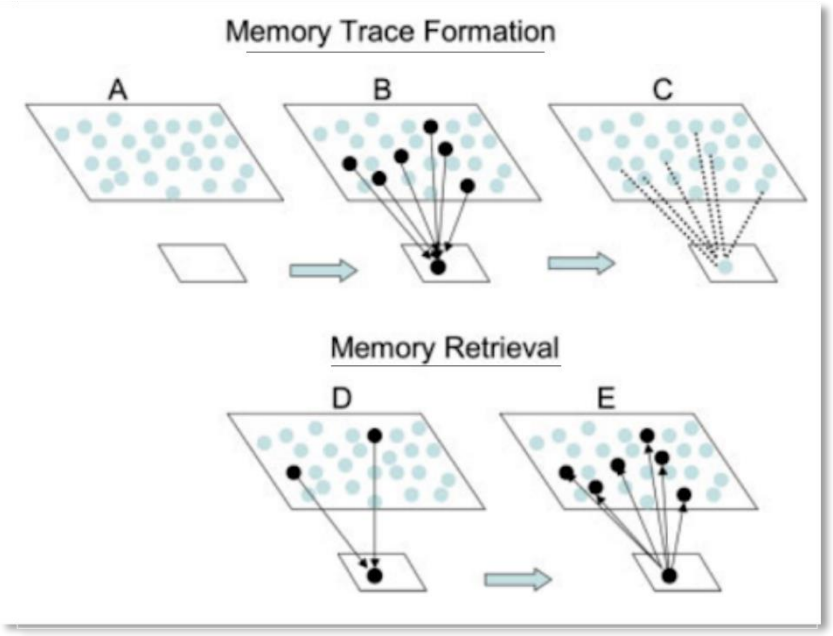


Figure 5. Memory formation **(A)** the top layer represents patterns of neocortical activity; the smaller layer represents the hippocampus. **(B)** A set of neocortical patterns projects to the hippocampus. **(C)** The memory for the experience is stored as strengthened connections among that hippocampal synapse activated by the input pattern. Memory retrieval: **(D)** A subset of the initial input pattern can activate the hippocampal representation. **(E)** When it occurs output from the hippocampus projects back to the neocortex to activate the entire pattern. Adapted from Teyler and Rudy, 2007.

This reinstatement of encoded-related activity during episodic retrieval has also been investigated with fMRI in combination of decoding approaches using MVPA[1] methods (Kuhl, Rissman, & Wagner, 2012; McDuff, Frankel, & Norman, 2009; Rissman & Wagner, 2012) providing additional support for the idea that the hippocampus is involved in the episodic retrieval arbitrating the reinstatement of patterns of activity learned during encoding (Johnson et al., 2009; Kuhl et al., 2012).

1 MVPA. Multi-voxel pattern analysis: Method that allows measurement of the similarity between patterns of fMRI activity distributed across a population of voxels, even when effects at the single voxel level are not statistically significant or spatially contiguous.

1.2.2 Event-Related Potentials at retrieval

Event-Related Potentials (ERPs) are important because they give us the opportunity to investigate how information is processed by the brain over time, from early sensory processing to recognition (Rugg, 2001). Unlike fMRI, ERP data does not allow us to allocate the neural origins of the measured activity at the scalp. However, the ERP approach does allow us to examine the temporality of the mental processes with a fine-grained resolution.

In a classic recognition test for episodes experienced in the past, participants had to discriminate between old (repeated) and novel items. The ERP correlates of episodic memory (also termed "Old/New effects") are commonly identified during these recognition tests, by contrasting ERP responses elicited by old items to those elicited by new items. Considerable effort has been made to elucidate the specific memory processes that cause old/new effects. This approach also led researchers to identify idiosyncratic neural responses associated with familiarity and recollection processes. These processes are often interpreted in favour of the dual-process model (Yonelinas, 2002). Familiarity is fast-acting, relatively automatic and does not provide qualitative information regarding memory. Familiarity-based recognition occurs when someone has a feeling of 'knowing' an item but cannot recall any further information on the episodic context in which the item was originally experienced. Recollection is slower, more effortful, and gives rise to consciously accessible information about the prior experience of the item and the context of that occurrence (e.g. Spatio-temporal context of the episode) (E. Tulving, 1985). Familiarity appears to be reflected by a negative potential, a waveform that arises for studied rather than non-studied items, and peaks at approximately 300-500 ms post-stimulus at frontocentral recording sites (**Figure 6**). This effect has been termed FN400 old/new effect or mid-frontal old-new effect (Mecklinger & Jäger, 2012; Rugg & Curran, 2007; for an alternative view of FN400 see Voss & Paller, 2008). The processes reflected by the FN400 have been the subject of intense debate. Most researchers agree that familiarity represents a content-free 'strength of evidence' signal. According to global matching models (Hintzman, 2004; Shiffrin & Steyvers, 1997) familiarity varies with the closeness of the match between the cues and previously studied information (Rugg & Curran, 2007). Other perspectives have suggested that FN400 does not reflect familiarity, a conscious process, but rather arises from an unconscious facilitating process of a repeated stimuli (perceptual or conceptual priming) (Paller, Voss, & Boehm, 2007; Voss & Paller, 2008) or initiation of memory search (Diana, Vilberg, & Reder, 2005; Johnson & Rugg, 2007). At the beginning of the debate, both sides acknowledged that the FN400 could reflect familiarity, conceptual priming or a combination of both processes (Paller et al., 2007; Rugg & Curran, 2007). However, as the debate continued, proponents of the conceptual priming hypothesis claimed that the evidence supporting

conceptual priming was contradictory to familiarity hypothesis (Voss, Lucas, & Paller, 2010), perhaps because this hypothesis could not explain why FN400 is not modulated by factors that affect conceptual priming (Stenberg et al., 2009) or that the topographies of both effects are different suggesting at least partially distinct neural generators (Bridger et al., 2012).

On the other hand, recollection is often defined as recognition accompanied by *source memory* (memory for a specific feature of the study context such as the location or colour of an item) and are more akin to cued recall. Findings from several studies have suggested that recollection has an ERP signature termed 'Late Parietal Effect' (LPE). The LPE takes the form of a phasic, positive-going waveform that peaks at 500-800ms after cue onset and frequently exhibits a parietal left-sided maximum (**Figure 6**). LPE amplitudes are often found to be greater for remember compared to know responses and know responses to new trials (Curran, 2000). The functional dissociation between the LPE and FN400 is highlighted in results from patients with restricted hippocampal damage, a structure related to affect recollection but not to familiarity. In these patients, FN400 is still present but LPE is absent (Addante et al., 2012). As the FN400, the functional significance of the parietal old/new effect is not well defined. Some suggestions are in line with the idea that they reflect processes that contribute to the representation of the recollected information (Edward L. Wilding & Rugg, 1996), or, on the contrary, indexing attentional orienting to recollected information (Wagner et al., 2005). Some evidence (Wilding, 2000) has suggested that the LPE varies according to the amount of information recollected, being more consistent with the first proposal (Rugg & Curran, 2007). Due to the characteristic scalp distribution of this effect, parallels between fMRI and ERP studies suggested that this effect comes from the lateral parietal cortex (Vilberg & Rugg, 2007; Woodruff, Hayama, & Rugg, 2006).

A third ERP component that has been attributed to reflect specific processes supporting recognition has also been reported in various studies in the form of late-onset positivity that has an onset at 800ms, maximal across right frontal electrodes, and appears to be driven by post-retrieval processing and not necessarily dependent on retrieval success (Roberts, Tsivilis, & Mayes, 2013). Post-retrieval processes referred to the monitoring and evaluation of the content of the retrieved information in relation to the goals of the retrieval attempt (Burgess & Shallice, 1996). Some authors have suggested that monitoring demands would be greater when the information available for a memory judgment was relatively impoverished due, for instance, to the absence of recollection (Henson et al., 1999), leading to uncertainty whether the retrieval has been successful (Rugg & Wilding, 2000) and generating these post-retrieval operations.

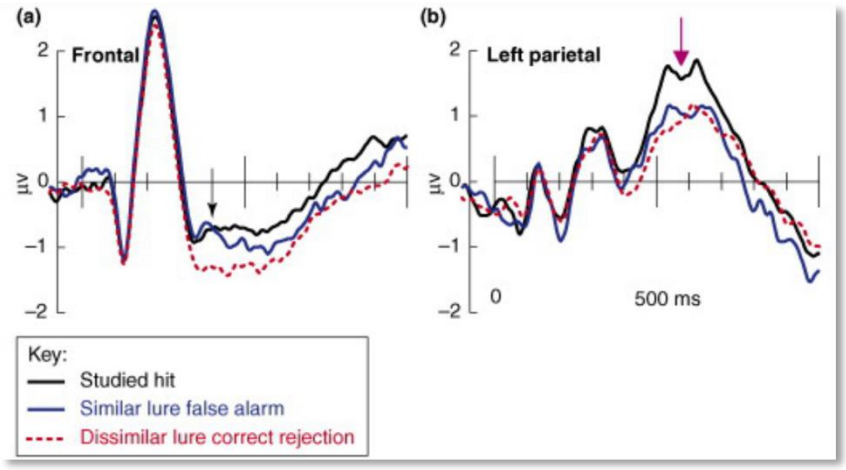


Figure 6. (a) Gran-average ERPs from frontal electrodes (average of electrode clusters including F3 and F4) with the FN400 Old/New effect indicated by the blue arrow. **(b)** Grand-average ERPs from left parietal (average of electrode cluster including P3) with the parietal Old/New effect indicated by the purple arrow. Adapted from Rugg and Curran, 2007.

1.2.3 The chronometry of retrieval

The conversion of a simple cue into a “full" memory is a process that could occur within a few hundred milliseconds. The combination of non-invasive electrophysiological recordings, such as EEG and MEG, and invasive techniques, such as iEEG, could give us insights into how sensory cues are converted into retrieved memories in real-time.

Figure 7 depicts on a mechanistic level, the temporal dynamics of memory recall since a cue is presented and the information travels across cortical pathways until it reaches the MTL. Intracranial EEG studies, that have employed simple old/new recognition tests, revealed that a response in the hippocampus starts at 500 ms after the presentation of the partial cue (Ludowig et al., 2008; Merkow, Burke, & Kahana, 2015; Mormann et al., 2005; Staresina et al., 2019). This cue elicits an initial ‘old/New’ signal (see Event-related potentials at retrieval), and if it is familiar, it would be able to reactivate hippocampal neurons that were assigned to the initial experience. As posited above, models of memory recall linked this process to hippocampal pattern completion actions, that if successful, would coordinate the reinstatement of the engram in the cortex (Staresina et al., 2016). In line with this, fMRI studies have also complemented to the electrophysiological techniques, by showing that activation levels in the hippocampus could indeed predict the extent of the cortical reinstatement (Ritchey, Wing, LaBar, & Cabeza, 2013; Staresina et al., 2012).

Invasive recordings have revealed how other parts of the cortex, such as the entorhinal cortex, are also implicated in the reinstatement of memory engrams during recall. The entorhinal cortex, with

entorhinal spikes following hippocampal spikes within 30 ms after the presentation of the cue (Staresina et al., 2019), could serve as the interface between intrahippocampal pattern completion and cortical engram reinstatement (O'Reilly & Norman, 2002). Computational studies have suggested (Teyler & Rudy, 2007) that reinstatement is mediated by the hippocampus indexing the entorhinal cortex, which in turn would index target cortical sites.

From 500ms to 1500 ms hippocampal-neocortical dynamics reinstate mnemonic patterns. During cued recall, sensory information pertaining to the cue enters the hippocampus in a feedforward manner and when successfully matched with and overlapping memory trace, hippocampal pattern completion processes reinstate the information back in the neocortex (Staresina & Wimber, 2019). Studies have shown (Linde-Domingo et al., 2019) that the cue-to-memory conversion, differed depending on whether the cue was visually perceived or recovered from memory. This could be explained by the existence of a *reverse flow of information* between perception and memory. If an object is perceived, perception followed the well-established forward stream, with perceptual features recovered online more rapidly than conceptual features. Nevertheless, when we need to reconstruct an object from memory without any visual aid, it has been observed that greater levels of reinstatement are needed to recall perceptual details as opposed to recalling categorical gist or conceptual features. Cued-recall seems to trigger a neural processing cascade that temporally prioritises abstract-conceptual over detailed-perceptual information. It has been shown that MTL preferentially back-projects to multisensory areas that contain higher-level abstract representations of an event (Schultz & Engelhardt, 2014) but does not terminate there, and can be found even in early visual cortex recapitulating visual processing at a later stage (Dijkstra et al., 2017).

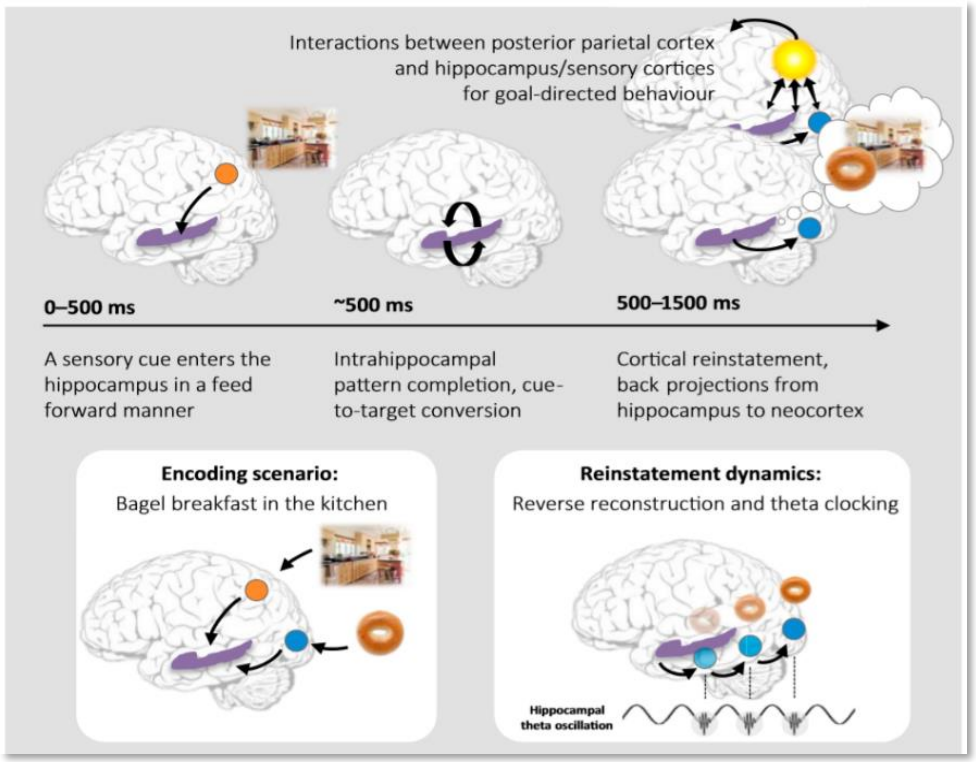


Figure 7. Top left to right: A memory cue enters the hippocampus in a feedforward manner, followed by pattern completion at approximately 500 ms after cue onset. From 500 ms onward, target memories are reinstated in the neocortex. Memory signals are projected to posterior parietal regions, with reciprocal interactions for maintenance and translation into goal-directed behaviour. Bottom left: Example of a unique event. Reinstatement propagates from the hippocampus back to neocortical regions that coded aspects of the original experience. This reinstatement cascade progresses along a feedback pathway that reconstructs an event in the reverse order from its original encoding. Each stage of this backward reconstruction process is characterised by bursts of neural activity in the reactivated neocortical areas and occurs in time-limited, rhythmic windows defined by the hippocampal theta rhythm. Adapted from Staresina and Wimber 2019.

1.2.4 Hippocampal theta oscillations at retrieval

As pointed out in the Encoding section, the brain oscillations that are thought to orchestrate the retrieval of information, in the medial temporal lobe, are ranged in the theta band (4-8Hz). Animal (Huxter et al., 2003; O'Keefe & Recce, 1993) and human studies (Düzel, Penny, & Burgess, 2010; Jacobs, 2014; Watrous et al., 2013) showed that theta rhythm supports learning and memory. The sequential firing of neurons along a theta cycle occurs in *gamma bursts*. Gamma is sometimes referred to as the brain's clock (Lisman & Jensen, 2013) which groups together cells that constitute a neural assembly (Dragoi & Buzsáki, 2006). Theta-gamma coupling has been found to increase during recall (Lisman & Jensen, 2013), when participants recognise a stimulus as old (Köster, Martens, & Gruber, 2019) or when recalling autobiographical events (Hebscher, Meltzer, & Gilboa, 2019), showing that theta could clock the timing of memory recall signals. Returning to the chronometry, from 500 to 1500 ms at the cue onset, the mnemonic content is thought to be

reactivated. In this time window, the decodability of perceived objects versus recalled ones was maximal at opposite phases of the theta cycle, with phase separation of information flowing into the hippocampus during encoding and out of the hippocampus during retrieval (Kerrén et al., 2018). Computational models (Hasselmo, Bodelón, & Wyble, 2002) have suggested that between these transitional phases the optimal time point for the perception-to-memory flip is provided, as argued in the previous subsection (see the chronometry of retrieval). Single-neuron recordings (Rutishauser et al., 2015) and iEEG studies (Griffiths et al., 2019) have also shown a temporal relationship between theta phase and neocortical reinstatement, in which an upstream region (e.g. hippocampus) initiates the recall process at the optimal retrieval phase of the theta cycle, followed by neocortical reactivation of the mnemonic content 200-300 ms later. Collectively, each theta cycle with the cue processing (within the first 500ms) and the target reinstatement (>500 ms) represent a gradual build-up process, that throughout each theta cycle, the entire episodic event would be reinstated. Theta rhythm is not limited to the hippocampus (Ketz, Jensen, & O'Reilly, 2015) and is thought to facilitate inter-regional communication between hippocampal-neocortical circuits providing discrete time windows for the progression of information from one level to the next. (Sirota et al., 2008; Staresina & Wimber, 2019).

In the context of scalp electrophysiological recordings, and its magnetic counterpart, theta rhythm modulation has been studied under the notion of power modulations given a retrieval task. These studies have shown that theta power could either display an increase or a decrease, and the reason for that still remains unclear (see Herweg et al., 2019 for a current debate). For instance, many studies have suggested that an increase of theta power could be related with successful retrieval (Backus et al., 2016; Osipova et al., 2006), meanwhile, other studies point out that power decreases might reflect higher-order memory control processes, such as inhibition or interference resolution (Hanslmayr et al., 2010) or the difficulty in the memory trace evaluation (Klimesch et al., 2006). However, as time passes and the memories become consolidated, down-regulation of interference and inhibition would no longer be needed (Irish et al., 2018) as there were not many items competing for recollection (Ferreira et al., 2019).

1.2.5 Neural correlates supporting memory retrieval

As previously stated, ERP studies were important to explore the temporality of the retrieval memory processes. However, these studies do not cover the neural sources that support memory retrieval. To that end, the fMRI technique is better suited. Two of the earliest fMRI studies using event-related designs compared fMRI signal when participants were recognising items on the bases of a familiarity or recollection process (Eldridge et al., 2000; Henson et al., 1999). The

consensus in these early fMRI studies and the following ones (Johnson & Rugg, 2007; Rugg & Vilberg, 2013) was that there is a 'core' recollection network of brain regions that includes the MTL, particularly in the hippocampus and parahippocampal cortex, along with the retrosplenial/posterior cingulate, medial prefrontal cortex and ventral posterior cortex (angular gyrus)(**Figure 8**).

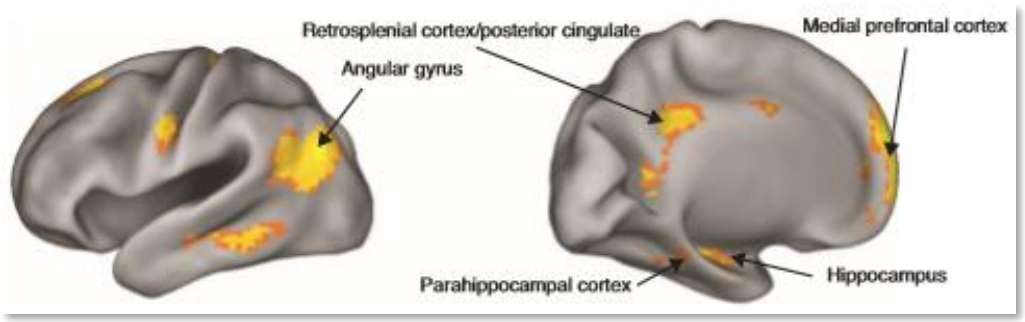


Figure 8. The putative core recollection network. Outcome of the contrast between correctly words endorsed as 'remember' versus 'know'. Adapted from Rugg and Vilberg, 2013.

This recollection brain network partially overlaps with the 'default mode network' originally identified by its greater activity during periods of rest rather than during stimulus-directed tasks (Schacter, Addis, & Buckner, 2008). The recollection network also overlaps with regions that are active when individuals mentally construct future-oriented and self-relevant scenarios (as episodic future thoughts: Addis, Wong and Schacter 2007). One important point of this network is that each cortical component exhibits structural and functional connectivity with the hippocampus (Aggleton, 2012), that plays a central role in episodic retrieval (see Theoretical frameworks), and mediated the reinstatement of patterns of activity elicited when the retrieved event was originally experienced (Ritchey et al., 2013). Although the functional roles of the different components of this network need to be elucidated, evidence suggests that successful recollection is associated with the engagement of a network of regions that is largely insensitive to how recollection is cued or the nature of the recollected information.

Another line of research aiming to understand the neural underpinnings of memory retrieval with fMRI used more realistic material to allow the exploration of autobiographical memories (AMs). These neuroimaging studies were much slower to develop compared with the similar laboratory-based studies previously explained. One reason for slower development was that the complexity of these studies challenged the notion of controllability required to run experimental research using neuroimaging techniques. These studies were often criticized by other cognitive neuroscientists as a 'waste of time'. Luckily, the development of new technologies and the new

perspective that this type of research has taken off in recent years, changed this view, and it is now considered a promising avenue that can offer valuable insights into memory.

First investigations aiming to study AMs showed that during retrieval, there was an involvement primarily of left-lateralized brain regions (Maguire, 2001; but see Svoboda, McKinnon, & Levine, 2006). Nowadays, it is a commonly accepted idea that AM recollection involves the interaction of different neural networks, comprising the medial and lateral PFC, the lateral and MTL (Hippocampus and parahippocampal gyrus), the ventral parietal cortex and the posterior cingulate cortex (Cabeza & St Jacques, 2007; McDermott, Szpunar, & Christ, 2009; Svoboda et al., 2006). These neural regions are referred to as the AM retrieval network. This network shares a close similarity with the core recollection network explained above in the laboratory-based tradition, showing that it may be possible that these networks are the same (see Laboratory-based studies versus AM studies).

The AM recollection network also overlaps with the default mode network, that seems to include two subnetworks (Andrews-Hanna et al., 2010): 1) the Medial PFC network that includes the dorsal medial PFC, the posterior cingulate and the ventral parietal cortices and 2) the MTL network that is made up of the hippocampus, the vmPFC, the retrosplenial and ventral parietal cortices. The Medial PFC network is recruited to a greater extent when making self-referential decisions, and the anterior midline regions when self-referential processes need to be activated. The MTL network has been related to constructing a scene based on memory, with the hippocampus associated with recollection processes during memory retrieval and activity within many of the MTL regions related to detailed recall and subjective recollection.

Another important network participating in AM retrieval is the frontoparietal or central executive network that includes lateral PFC, anterior cingulate and inferior parietal cortices and is associated with adaptive cognitive control processes (Vincent et al., 2008) and decision-making (Dosenbach et al., 2007). Networks are shown in **Figure 9**.

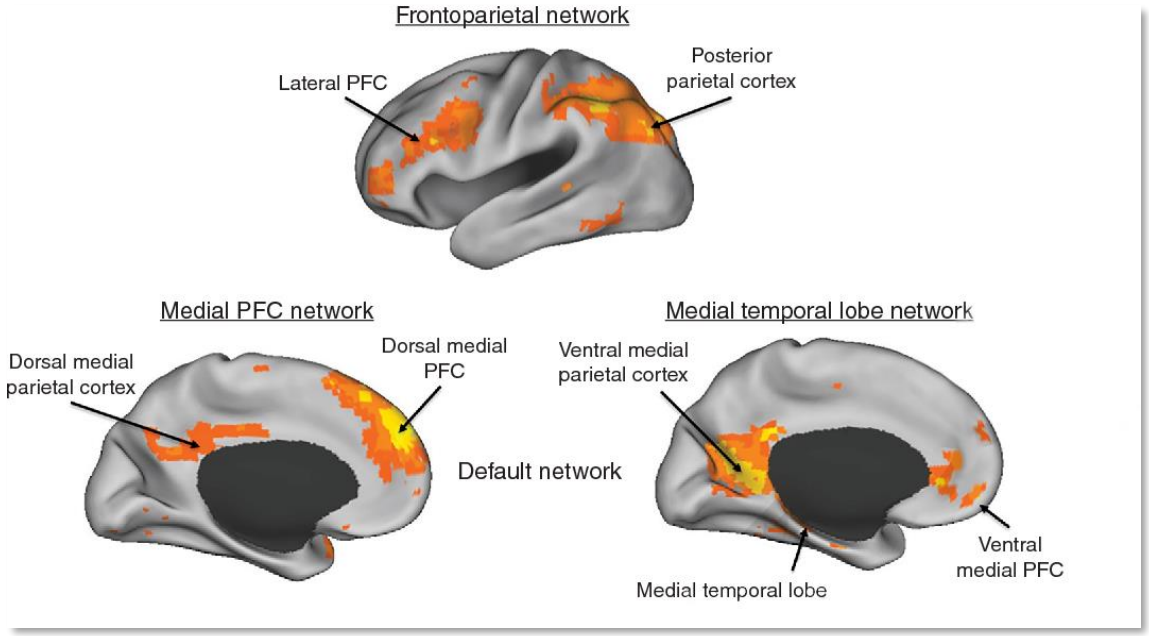


Figure 9. Large-scale networks contributing to autobiographical memory. Adapted from St. Jacques and Brigard, 2015.

In addition, three parietal regions have also been found to support memory processes in the context of AMs: the precuneus, the mid-cingulate cortex and the posterior inferior parietal lobule/dorsal angular gyrus. These three regions reflect mnemonic processing during initial encoding and later retrieval, forming a functional network known as the Parietal Mode Network (PMN). Some studies have related greater activation of the PMN to the processing of familiarity (Gilmore, Nelson, & McDermott, 2015) but not many of the autobiographical memory studies include it as part of their activation networks. Svoboda et al., 2006 in their meta-analysis, included it as one of the tertiary regions, meaning that it was found in less than 5 studies reviewed. The precuneus (left) has been linked to the retrieval of specific autobiographical memories (Addis, Moscovitch, Crawley, & McAndrews, 2004) and to the initial access to personal memory representations (Mazzoni et al., 2019).

How are these networks engaged at the time of retrieving a memory?

St. Jacques, Kragel and Rubin 2011 observed that the recruitment of the frontoparietal network was isolated to the initial scene search and the construction of AM retrieval, whereas, default mode network activation extended into the elaboration period. The PFC network is the essential network that is in charge of driving the interaction among these networks. Furthermore, memory accessibility and recollection could alter the connectivity amongst these networks, with recollection modulating the influence of PFC on the MTL network during elaboration. This

suggests that greater connectivity between the subsystems of the default mode network supports greater re-experiencing during the retrieval of AMs. Analysing the recruitment of the AM neural networks and the interaction of these networks could be crucial to help to distinguish the AM retrieval from other similar tasks such as prospection or theory of mind (Spreng et al., 2010).

1.2.6 What are the similarities and differences between the two traditions: laboratory-based and AM studies?

There is not an extensive bibliography examining this question, however, what we could infer is that laboratory-based methods offer strict experimental control over AM studies. Variables could be manipulated and controlled through the encoding and retrieval phases of an experiment. As McDermott, Szpunar, and Christ 2009 pointed out, one of the downsides of the laboratory tradition is that ecological validity is compromised. *How well does a person's recognition of whether the word 'HAM' had been read 10 min prior, inform the understanding of the process underlying recollection of life events?* Life events are more complex, constructive and richer in sensory details, and most of the time they are emotional and self-oriented. Laboratory-based methods also differ in the timescale of the events that tend to be in the scale of minutes/hours compared to autobiographical methods that could last weeks or years. The elaboration time window of the memory could be also extremely variable, going from one second or two at the time to take a recognition memory decision in lab-based methods, and from 8 to 12 seconds when we need to construct an autobiographical memory. The methodological choice is also important between these tasks, as old/new recognition memory studies tend to be selected in laboratory-based methods and cued recall or verbal recall are likely to be used at the autobiographical ones. AM studies could also investigate the recollective qualities of event memories, such as emotion or vividness, which is difficult to capture in the retrieval of laboratory stimuli.

Several studies have tried to contrast both traditions (Cabeza et al., 2004; McDermott et al., 2009; Nyberg et al., 2002) with varying results. Cabeza et al., 2004 encountered many similarities between the two networks noting differences in the direction of higher level activation for the autobiographical memory task within regions contributing to self-relevant processing (medial prefrontal cortex), visual-spatial memory (occipital and parahippocampal regions) and recollection (hippocampus). Nyberg et al., 2002 found little activation in common when contrasting traditions. McDermott, Szpunar, and Christ 2009 performed a whole-brain level meta-analysis of the likelihood of activations across literature, and they found that the regions emerging from both traditions' studies were nonoverlapping and different brain networks contributed to the two tasks, with caveats about the methodology and the type of cueing used in the studies. In

another recent study (Roediger & McDermott, 2013b) these authors highlighted a study with people with HSAM[2] (Patihis et al., 2013) that demonstrated average performance of remembering laboratory events compared with their remarkable accurate capabilities of remembering their own past. This incomplete puzzle tells us that there is a need to develop more studies that could bridge both traditions in order to shed light on the networks that support autobiographical retrieval. In study 2 (see Chapter 4), I proposed a new methodological and naturalistic approach combined with a lab-based paradigm that could help to put together some pieces of the puzzle. In study 3 (see Chapter 5) I presented some fMRI data in which we tested this paradigm, and we observe and discuss the involvement of the AM networks.

1.2.7 Neural correlates of recent versus remote personal episodes

One question that remains to be addressed in the literature is whether the neural correlates of remote and recent memories change as the delay between encoding and retrieval increases. It is thought that some information is lost as time passes following a decay rate that is maximal after learning and then gradually declines (Ebbinghaus, 2013; Wixted, 2004). However, in spite of this expected decrease, models of memory consolidation (Alvarez & Squire, 1994; Nadel & Moscovitch, 1997) tried to explain the existence of 'a remoteness effect'. The Remoteness effect, as stated by the standard consolidation model (SCM), refers to the prediction of greater hippocampal activity for recent autobiographical memories compared to remote autobiographical memories (Squire, 1992). SCM posited that the hippocampus has a time-limited role in the storage and retrieval of AMs and after consolidation, these memories become more dependent on neocortical areas (Alvarez & Squire, 1994; Teyler & DiScenna, 1986; Winocur & Moscovitch, 2011). On the other hand, the multiple trace theory (MTT) supports that the hippocampus has a permanent role in the retrieval of vivid memories. MTT encourages the inexistence of a remoteness effect because both, recent and remote, would elicit similar hippocampal activity. Most of the existent studies did not find the remoteness effect, therefore supporting MTT theory (Addis et al., 2004; Gilboa et al., 2004; Maguire, 2001b; Maguire & Frith, 2003), but see (Nadel & Moscovitch, 1997; Piefke et al., 2003).

2 HSAM: Highly superior autobiographical memories. Refers to a condition that leads people to remember an abnormally large number of their life experiences in vivid detail.

When does a memory change from recent to remote?

Research on how brain responses at retrieval are modulated to the passing of time from encoding has identified several issues that should be taken into account. Cabeza & St Jacques, 2007 proposed that the hippocampal activity could reflect re-encoding processes because, in studies of retrieval from the remote past, participants are not only retrieving but also incidentally encoding the test material for possible later use (Gilboa et al., 2004; Squire & Bayley, 2007). Moreover, a comparison between recent and remote memory must consider that memories from different time periods differ not only in age but also in accessibility and vividness. Remoteness effect could disappear when the vividness factor would be entered as a covariate in fMRI analyses (Addis et al., 2004). Besides, the amount of time offered to the participants for AM retrieval is also determinant. Shorter retrieval times enable the retrieval of details for recent but not for remote memories, leading to a remoteness effect (Maguire & Frith, 2003), whereas longer retrieval times enable the retrieval of details for both kinds of memories reducing or eliminating the remoteness effect (Ryan et al., 2001).

In the hippocampus and the other MTL structures, information about recent and remote was present to a similar degree, but despite the hippocampus' role for recent and remote AMs in equal measure, the information seems to have a spatial bias, with higher classification accuracy in the posterior hippocampus for remote compared to recent memories (McCormick et al., 2015). This study suggests that at retrieval, the hippocampus could be the place to assemble the different pieces of information stored at encoding into a coherent form, and that remote memories relied more on this process than recent memories.

Other brain areas apart from the hippocampus, as the retrosplenial cortex (Gilboa et al., 2004; Piefke et al., 2003; Steinvorth, Corkin, & Halgren, 2006), have been consistently proposed to be sensitive to the age of memories. One of its roles could be related to the construction of generic visual representations, retrieval of personal familiar information, emotional processing and vivid recollection. Prefrontal cortex regions have also been suggested to represent specific autobiographical memories, obtaining more variable results of activations depending on the age of the memories (Niki & Luo, 2002; Rekkas & Constable, 2005). The vmPFC has been found to be the part of the PFC processing information about recent and remote autobiographical memories. A recent study (Bonnici et al., 2012) has revealed that information about remote autobiographical memories were more readily detectable in vmPFC and temporal pole compared with recent memories. This could also be linked to the necessity of requiring a schema to guide them, as suggested in the Encoding section, and possibly monitor the results to avoid confabulation (Gilboa

et al., 2006). Increased functional connectivity between the hippocampus and PFC has been reported during reconstruction and elaboration of AMs (McCormick et al., 2015).

The idea that neural correlates supporting the retrieval of consolidated memories as a function of their remoteness from encoding has also been explored by means of ERPs. However, these studies have been tested at extremely short time delays between encoding and retrieval (24 hours interval) (Curran & Friedman, 2004; Jaeger et al., 2009; Wolk et al., 2009) and at a 4-week delay (Roberts et al., 2013; Tsivilis et al., 2015) and they did not find differences suggesting that this effect was not modulated by delay (Roberts et al., 2013). Changes in these neural correlates may be due to a direct effect of time on systems consolidation (the details remembered drop because of the existence of normal forgetting) or the indirect effect of time on the quality of memories (subjective confidence or memory strength). Some studies (Jaeger et al., 2009) have found qualitative changes at comparing ERPs suggesting that ERPs may be sensitive to consolidation processes. Other studies (Dudukovic & Knowlton, 2006) posited that there is a drop only in the remember responses and a smaller decliner at familiar responses over time. On the other hand, some studies have found (Tsivilis et al., 2015) that FN400, related to familiarity-based recognition (see Event-Related potentials at retrieval subsection), is not a short-lived effect and can last at least four weeks after the encoding of the information and nor the topography nor the amplitude of the effect showed sensitivity to memories' age. See **Figure 10** for a comparison of FN400 and LPE over time.

Taken together, more studies controlling for factors such as the length of the retention interval, the memory accuracy or the amount of recollected information are needed to understand the neural correlates of memory retrieval for real-life experiences.

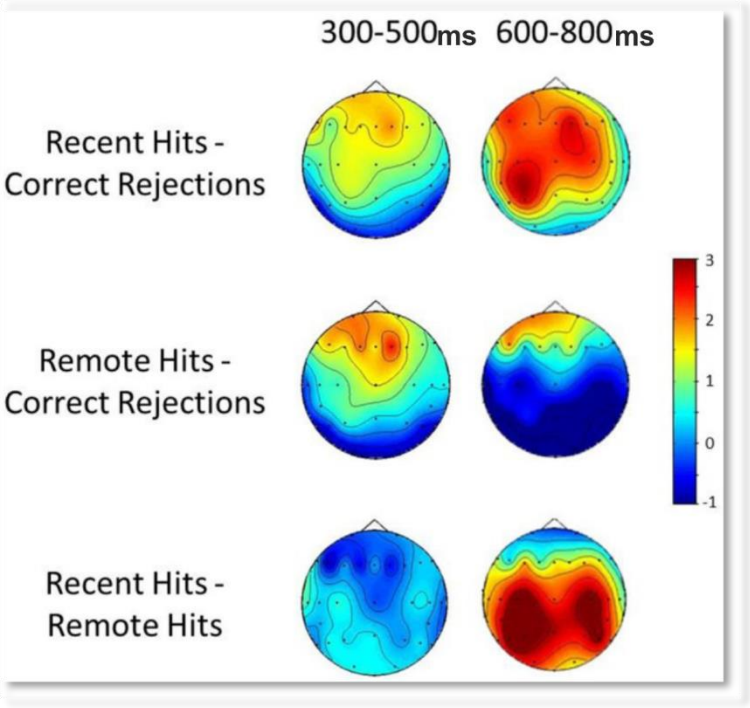


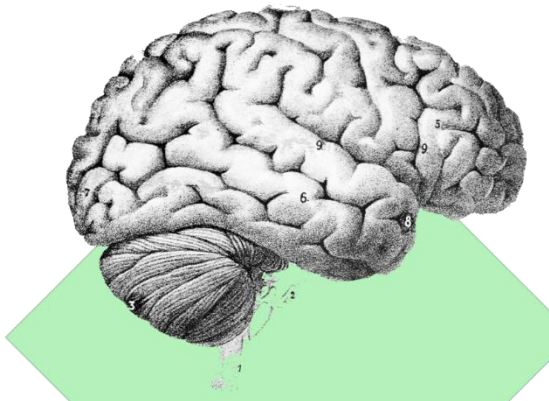
Figure 10. Topographic distribution difference maps for the 300-500ms (related to familiarity) and 600-800ms (related to recollection) periods. Top row: Recent Hits-Correct Rejections; Middle-row: remote Hits-Correct Rejections; Bottom row: Recent Hits-Remote Hits. Adapted from Tsivilis et al., 2013.

1.2.8 Studying memory retrieval in neurological population

Memory impairment is one of the most devastating results of a neurological disorder. Memory depends on encoding, storing and retrieving new information and, as posited in this chapter, the hippocampus and its connections with other MTL and neocortical regions are crucial to these processes. Damage to MTL structures produces amnesia that impairs the encoding of new information and the retrieval of recently encoded information (Scoville and Milner, 1957). Damage to the PFC causes impairment in patients at recalling specific information (as contexts), overcoming interference, ordering information at retrieval and retrieving with limited cue support (Szczepanski & Knight, 2014). Successful remembering in everyday life also requires the ability to assimilate new information, pay attention to the environment (both to ensure encoding and evoke the retrieval of the information) and self-monitor responses (to avoid repetition, judge correctly). All these processes rely on widespread networks (along with cortical and subcortical structures) that could be damaged in neurological patients making the collaboration with them fundamental for understanding the mechanisms of remembering.

In the last decade, new technologies have been massively developed and cognitive neuroscience has taken advantage in trying to develop more effective interventions for memory-impaired individuals. One of these new advances has been prosthetic devices that outsource memory and

could be promising in order to help patients to improve their recalling abilities. One example of this new breakthrough has been developed at the University of Toronto under the name of *Hippocamera* (http://www.hippocamera.com/). This device is an app designed in two modes: record and replay, that tries to mimic hippocampal replay to help Alzheimer's patients to relearn memories of their everyday life or staving off further decline. In Barcelona, a similar program called *Re-memory* (http://www.rememory.cat/en/projecte-2/) is trying to improve memory with patients with mild-cognitive impairment. There are still no conclusive long-term results. However, everything indicates that promising results are on the horizon.



Chapter 2

Research Aims

Chapter 2: Research Aims

2.1 General objective

The research questions and the experimental studies of this thesis are based on the theoretical framework and empirical evidence outlined in the previous chapter. **The main aim of this work is to shed new light on the cognitive processes and neural mechanisms that support the formation and the retrieval of memories in humans in ecologically valid contexts.** Ecological validity is an important topic that has been debated in the human neurosciences research field over the recent years. Although maintaining laboratory-based control is needed for scientific progress, the work described in this thesis represents an effort to develop novel approaches and to provide empirically grounded evidence for research questions about human memory that are difficult to assess in the laboratory alone.

2.2 Research questions and hypotheses

This thesis aims to bring more knowledge to the field and fill critical gaps in the understanding of two important cognitive operations in the study of human cognition:

2.2.1 How does stored knowledge influence the formation of new memories? Or in other words, how do we integrate novel inputs that overlap with existing structures of memory networks?

The first study (see chapter 3) combined EEG with behavioural data to understand how novel experiences that overlap with previously acquired structures of knowledge are integrated into long-term memory. The aim of this study was to investigate whether the nature of the overlapping representation, either at the episodic or at the semantic level, between existing and novel inputs affected how they were integrated into a relational memory network. The hypothesis was that integrative encoding was effective and hippocampus-dependent in both cases, although it relied on distinct neural mechanisms that could be observed during encoding itself.

2.2.2 Can we study the cognitive and neural underpinnings that support the retrieval of real-life autobiographical memories at individual level?

To address this question, we developed a new experimental approach that allowed the recording of a large sample of individual experiences extracted from real-life episodic routine and then to use these records as cues to explore how autobiographical memories were retrieved (see Chapter 4). Being successful in such query relied on the possibility that we could address the following aims and questions:

2.2.2.1 To be able to acquire samples of individual real-life experiences prospectively and automatically

Simulating ecological valid scenarios in the laboratory has been a challenge in the last decade. The vast majority of behavioural and neuroimaging studies have used laboratory stimuli. Although the use of this lab-based material allows solid experimental control, real-world experiences contain features that have more personal relevance and tend to have richer properties. Most of the experimental approaches to explore autobiographical memories require the participants to register and then recall targeted memories of their own life through the use of diaries (Burt, Kemp, & Conway, 2003) or voice recordings (Levine et al., 2004; Svoboda et al., 2006). However, sampling methods that rely on participants' active recording of selected experiences cannot guarantee that these memories are biased by inherent cognitive operations that require the selection and organization of the material that conforms to the sampled experience. To avoid this concern, we need methods that allow the prospective recordings of real-life experience in an automatic manner, ahead of participants' active control. The progressive incorporation of wearable technologies, such as cameras, can give the participants the opportunity to automatically capture images of their life events, and can later be used by the experimenters as probes to assess retrieval processes of these real-world autobiographical memories. In study 2 (see Chapter 4), individual photographs of each participant were obtained by wearable cameras and were used as a cue to engage into the retrieval of autobiographical memories.

2.2.2.2 To develop and validate a protocol that engages the retrieval of autobiographical memories and that could be applied in clinical scenarios with neurological patients.

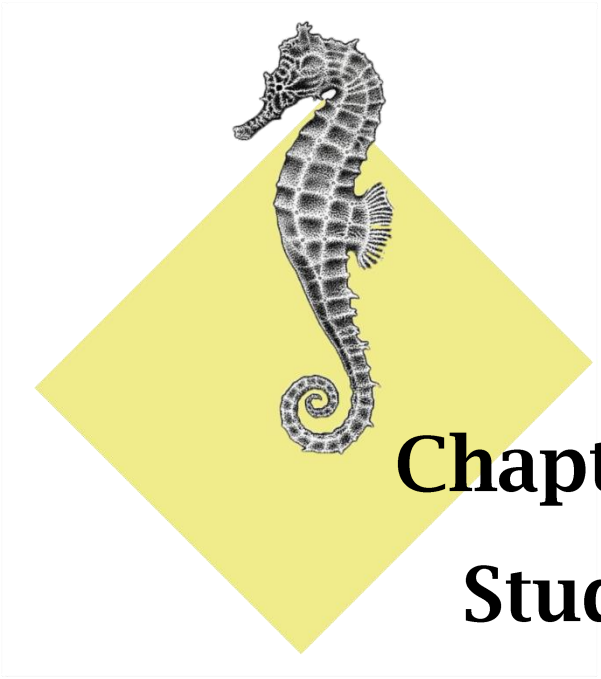
The collection of stimuli, in this case photographs, is not solely based on camera use. To obtain an individual photo collection of each participant we had to create and implement a protocol with different phases: First, a period of one-week data collection was stipulated. After that, data management needs to be performed with photo selection through an algorithm classifier, photo distribution over different tests, and incorporate the resulting photographs in the experimental design to be tested at three different time periods. The protocol was validated to ensure that the selection of photographs and the experimental design clearly engaged real-world autobiographical memories in healthy participants. With this protocol validated in healthy controls, the final objective was to apply the protocol in epileptic patients that are surgery candidates.

2.2.2.3 To explore the neural responses supporting the retrieval of autobiographical memories over time, using personal stimuli compared to lab-stimuli.

The majority of episodic retrieval studies have used laboratory stimuli as memory cues. However, the encoding of events in naturalistic scenarios has revealed that autobiographical stimuli have more personal relevance and are more complex when compared to lab-based studies (Chow & Rissman, 2017). In study 2 (see Chapter 4), we used personal stimuli to explore, through an old/new recognition test, the neural mechanism underlying the retrieval of autobiographical memories. We also used lab-based stimuli, to evaluate possible differences in participant's retrieval processes. Based on previous literature that has demonstrated that theta oscillations are engaged during retrieval and are responsible for learning and memory (T. Curran, 2000; Nyhus & Curran, 2010; Rugg & Curran, 2007), theta oscillations are the best candidate to track the temporal dynamics of retrieval and shed more light on how this process works. Based on ERP research, it is expected that we would observe diverse frontal or parietal effects depending on the behavioural response of the participants, linked to familiarity or recollection responses (T. Curran, 2000) and explore how these effects could change as time passes.

2.2.2.4 Implementation of our approach at a clinical level.

In the second study (see Chapter 4) we implemented our autobiographical recognition protocol in a single case of a condition called Aphantasia. Aphantasia is described as a reduced or absent voluntary image (Zeman, Dewar, & Della Sala, 2015). In this study we aimed to understand how visual imagery could impact the retrieval of autobiographical memories. In the third study (see Chapter 5) we presented fMRI preliminary data of a control sample of five participants. We aimed to explore if our experimental protocol would elicit MTL/hippocampus activity during the retrieval of autobiographical memories. In order to do this, we applied the old/new recognition paradigm from study 2 (see Chapter 4). Evidence from fMRI studies has revealed that retrieval effects could emerge from a network termed the *autobiographical retrieval network* (Cabeza & St Jacques, 2007). This network is comprised of the engagement of different subnetworks: the medial PFC network, the MTL network (Andrews-Hanna et al., 2010) and the frontoparietal network (Vincent et al., 2008) that promote the reconstruction of autobiographical memories. fMRI may be better-suited to track the spatial dynamics at the time of retrieval. Therefore, the application of our autobiographical protocol with fMRI methods could be very useful in patients in investigating how lesions in the MTL/hippocampus could affect the retrieval of personal memories.



Chapter 3

Study 1

This study corresponds to:

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Chapter 3: Study 1

Theta rhythm supports hippocampus–dependent integrative encoding in schematic memory networks

Integrating new information into existing schematic structures of knowledge is the basis of learning in our everyday life as it enables structured representation of information and goal-directed behaviour in an ever-changing environment. However, how schematic mnemonic structures aid the integration of novel elements remains poorly understood. Here, we showed that the ability to integrate novel picture information into learned structures of picture associations that overlapped by the same picture scene (i.e., associative network) or by conceptually related scene information (i.e., schematic network) is hippocampus-dependent, as patients with lesions at the medial temporal lobe (including the hippocampus) were impaired in inferring novel relations between pictures within these memory networks. In addition, we observed more persistent and widespread scalp electroencephalographic (EEG) theta oscillations (3-6Hz) while healthy participants encoded novel pictures into schematic memory networks, suggesting that theta may reflect distances between elements within a representational network space. Finally, we found higher similarity values for neural activity patterns elicited by novel and related events within associative networks, thereby suggesting that neural reactivation promoted the integration of new information into existing memory networks when elements within a memory network are linked by direct associations. These findings have important implications for our understanding of the neural mechanisms that support the development and organization of structures of knowledge.

3.1 Introduction

Experiences often overlap in content, presenting opportunities to integrate them into mnemonic networks. These mnemonic networks share certain characteristics, such as plasticity and hierarchical or schematic organisation (Eichenbaum, 2017), which enable structured representation of information and goal-directed behaviour in an ever-changing environment (McKenzie et al., 2014). However, how such schematic mnemonic structures aid the integration of new information remains unclear.

The standard approach to examining integrative encoding into memory networks has been to train subjects on separate events that share common elements (e.g., AB and BC) and then test for the associative network (ABC) via assessment of knowledge about the indirectly associated network elements (AC). This research has shown that the hippocampus and the prefrontal cortex (PFC) are not essential to training on individual associations (AB and BC) but do play a critical role in integrating information across related associated events (AC) (Dusek & Eichenbaum, 1997; Greene et al., 2006; Heckers et al., 2004; Preston et al., 2004; Schlichting & Preston, 2016). Leveraged by the use of neuroimaging techniques with fine-temporal resolution, such as magnetoencephalography (MEG) and electroencephalography (EEG), recent studies have also shown that the integration of novel events into an existing associative memory network relies on hippocampus-driven oscillatory activity in the theta range (3-8Hz) (Backus et al., 2016; Sans-Dublanc et al., 2017). Thus, while this approach has provided valuable insights into the neural underpinnings supporting the formation of associative memory networks, we still lack understanding of whether a similar neural framework can be generalized to more complex scenarios, akin to real-life environments, whereby schematic structures of knowledge foster the rapid assimilation of new events (Packard et al., 2017; Tse et al., 2011; Van Kesteren et al., 2010; Van Kesteren et al., 2012).

To address this issue, we designed a two-phase task wherein participants first learned an intermixed set of picture associations (i.e., face-scene) and then learned another set that overlapped with the first set with a common scene (i.e., associative network condition) or with scene images that depicted the same conceptual information (i.e., schematic network condition) and subsequently generalized to novel stimulus combinations (**Figure 11**).During learning phase 1 (LP1), participants learned to associate a face with a scene by choosing which of two scenes went with the face, and then receiving feedback. While each face-scene association was learned individually, there was partial overlap across events. Some pairs overlapped with a common face picture (A-B and A-C; associative network condition) and other pairs with scene pictures from the same semantic category (A-B_1 and C-B_2; schematic network condition) (**Figure 11A**). By the end

of LP1, we expected that participants would have successfully learned the individual associations and integrated them based on their relational network properties, namely associative or schematic (**Figure 11D**).

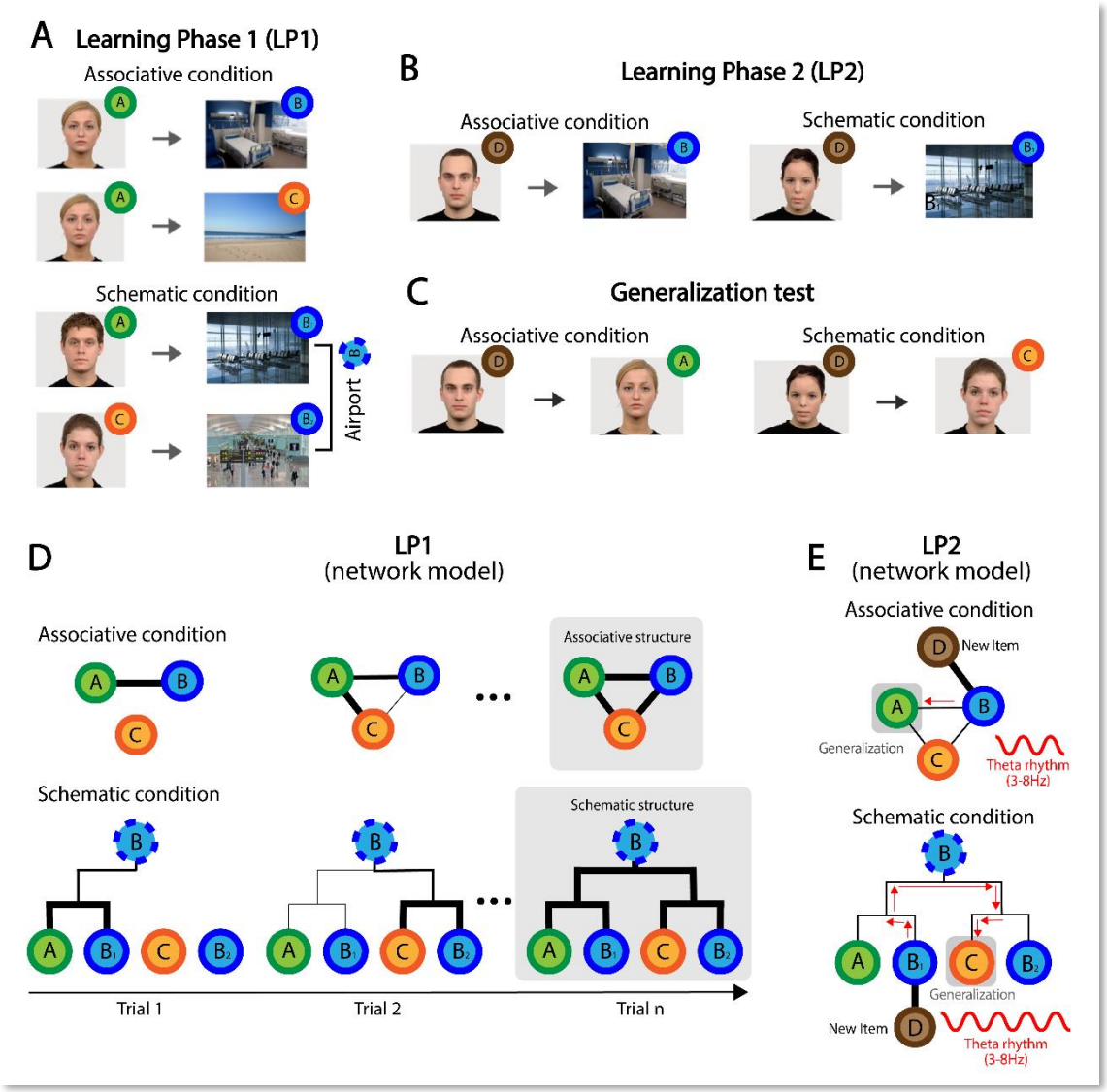


Figure 11. Experimental design and mnemonic network models. (A) In LP1, participants encoded pairs of face-scene images. Picture pairs were organized so that some of them shared the face image (Associative condition) and some shared the scene semantic context (Schematic condition). Picture pair conditions were presented intermixed during LP1. **(B)** In a following LP2, participants had to learn novel face-scene pairs. All pairs used face images that overlapped with one of the pair images from each subset in LP1. Picture pair conditions were presented intermixed during LP2. **(C)** Participants' memory for LP1 and LP2 picture pairs was subsequently tested using a two-alternative forced choice paradigm that included directly learned association trials ("trained") as well as inference trials that tested participants' ability to generalize. Specifically, "generalization" trials tested whether participants would choose A/C, encoded in LP1, when presented D, encoded in LP2. **(D)** Hypothesized memory representation model accounting for each of the learned picture sets in the associative and schematic conditions throughout LP1. Thick lines between elements depict picture pairs presented in a given trial. Thin lines depict connections of picture pairs established during learning via integrative encoding. At the end of LP1, we hypothesized, several

corresponding memory networks were acquired, and their structure reflected an associative or a schematic typology. **(E)** Diagram depicting our hypothesis that the integration, during LP2, of a novel element in the establish memory networks from LP1 promoted the binding of a connected set of nodes within the network and that this process was signalled by theta oscillations. Face images used in our study were taken from Minear et al. (2004), which provide a face image database with the authorization for publication for research purposes.

To assess whether these two mnemonic network structures influenced integrative encoding of new information, we next asked participants to encode a novel set of face-scene picture associations (i.e., learning phase 2, LP2), wherein each scene picture corresponded to a scene from the mnemonic picture set learned in LP1 (**Figure 11B**). Thus, we expected that the overlap between scene images (B and B_1 in **Figure 11B**) would induce the integration of the new face images (i.e., D) into the specific memory network learned in LP1, thereby promoting generalization (**Figure 11E**). Thus, in LP2, trials from the two conditions were similar in their configuration (face – scene) and in the content of the picture that overlapped with picture sets from LP1 (i.e., scenes), thereby allowing to infer that any possible difference in the elicited neural patterns to be attributed to the integrative encoding mechanisms linked to the memory network properties established in LP1. After LP2, participants were tested using a two-alternative forced-choice paradigm that included directly learned association trials ("trained") as well as inference trials that tested participants' ability to generalize. Specifically, "generalization" trials tested whether participants would choose A/C, encoded in LP1, when presented D, encoded in LP2 (**Figure 11C**), thereby assessing whether they had successfully integrated LP2 events into the related memory structures acquired in LP1.

Here, we aimed at examining whether events encoded in LP2 elicited different theta oscillatory patterns as a function of whether they were linked to associative or schematic memory networks acquired in LP1. Previous findings have shown that theta activity encoded representational distances in a spatial space (Bush et al., 2017; Vass et al., 2016) but also in the semantic and temporal word space (Solomon, Lega, Sperling, & Kahana, 2019b), supporting the idea that theta underlies the navigation through a general-domain cognitive map in the hippocampus. In the item recognition literature, it is generally agreed that the presentation of an external stimulus initiates a processing cascade that starts with low-level perceptual features in early visual areas, and progresses to increasingly higher levels of semantic integration and abstraction along the inferior temporal cortex (Carlson et al., 2013; Cichy, Pantazis, & Oliva, 2014; Clarke & Tyler, 2015; Lehky & Tanaka, 2016; Martin et al., 2018; Serre, Oliva, & Poggio, 2007). Similarly, the notion that external input processing follows a hierarchical information processing stream has been a hallmark in major theories of human memory networks (e.g., Collins & Quillian, 1969). More specifically, these models maintain that nodes in the memory network are represented in a

hierarchical fashion, and that activation also spreads in a hierarchical fashion in the network, that is, from a node to an immediately lower node and then to a node still lower in the hierarchy. For instance, activation of plant would first spread to flower and then to rose. One of the major assumptions in spreading activation model is that the amount of activation reaching a node depends on the distance from the source of activation, which received empirical support from studies investigating reaction time data in adult participants (Sharifian & Samani, 1997). Thus, in line with this notion, we hypothesized that the integration of new items into schematic memory networks would involve larger spreading activation than for when new items can be integrated into an associative memory network, and that this would be reflected as more persistent theta activity elicited by each of the events in LP2 (**Figure 11E**). Second, prior literature has emphasized that inferential learning relies on the reactivation of memory events related to a network (e.g., Zeithamova, Schlichting, & Preston, 2012). In the current study, we implemented a time-resolved neural similarity analysis (e.g., Silva, Baldassano, & Fuentemilla, 2019; Sols et al., 2017) to elucidate whether LP2 events elicited the reactivation of elements within a schematic and associative network. And third, we examined the critical role of the hippocampus in integrative encoding for associative and schematic memory networks by comparing behavioural data from chronic epileptic patients with lesion at the hippocampus with data from a matched control sample.

3.2 Material and Methods

Participants

Experiment 1: Healthy adults. Forty right-handed healthy volunteers (34 women) participated in experiment 1. The mean age of the participants was 23.62 (SD = 2.98 years). All the participants included in the study reported no history of medical, neurological, or psychiatric disorders, and no drug consumption. All subjects were volunteers, gave written informed consent, consented to publication, and received financial compensation for their participation in this study. All participants had normal or corrected-to-normal vision. The study was approved by the Ethics Committee of the University of Barcelona.

Experiment 2: TLE patients. A group of fourteen patients (6 women; mean age = 47.36 years old (SD = 12.54); mean years of education was 13.36 (SD = 5.40)) with refractory mesial temporal lobe epilepsy (TLE) caused by different aetiologies was recruited following a pre-surgical evaluation at the University Hospital of Bellvitge (**Table 1**). All patients had sustained damage to the right or left anterior medial temporal lobe structures, including the hippocampus. In all

patients, verbal and non-verbal intelligence was assessed using the Weschler Memory Scale, and the mean IQ was 95.54 (SD = 15.9). None of them showed mental disabilities (IQ under 80). Patient diagnosis was established according to clinical, EEG, and magnetic resonance imaging or FDG18PET. All of the patients underwent neurological and neuropsychological examination, continuous video-EEG monitoring, and structural and functional neuroimaging (MRI and PET). Patients were included in the study when the clinical data, EEG findings, and neuroimaging data suggested unilateral mesial TLE. All patients had: 1) seizures with typical temporal lobe semiology that were not controlled with antiepileptic drugs, 2) EEG patterns concordant with mesial temporal lobe epilepsy, and 3) neuroimaging data supportive of hippocampal involvement in seizure generation. None of the patients suffered a seizure during the experimental task or 24 hours before the task, and all the patients were on habitual anti-epileptic drug regimens. The study was approved by the Ethical Committee of the University Hospital of Bellvitge. Informed consent was obtained from all the patients before participation in the study.

Experiment 2: Healthy controls. The control group consisted of fourteen participants with no history of neurological disorders. Control participants were individually matched to TLE patients. Mean age of the control group was 46.64 years old (SD = 12.42) and mean years of education was 13.71 (SD = 5.41). No differences were found between groups in terms of age ($t(26) = 0.15$, $p = 0.89$) or years of education ($t(26) = -0.17$, $p = 0.86$). Informed consent was obtained from all subjects before their participation in the study.

Experimental procedures

Stimuli. Stimuli consisted of 24 images of Caucasian (half women) non-expressive faces (F) from Radboud database (Langner et al., 2010) and from UT Dallas database (Minear & Park, 2004) and 48 scene (S) images selected to depict 48 real-life contexts, half of them from indoor contexts (bars, airports, hospitals, supermarkets, kitchens, bakeries, hairdresser's, clothing stores, locker room, cinema, bus stop, ice-cream shop, computer store, campsite, jail) and the other half from outdoor contexts (parks, landscapes, waterfalls, mountains, caves, beaches, lakes, forests), from SUN database (Xiao et al., 2010).

The faces were distributed through LP1 (8 for the episodic and 16 for the semantic experimental condition), LP2 (8 for each experimental condition), generalization (8 for each experimental condition), and trained test (16 each experimental condition). Scene context images were distributed over LP1 (16 for each experimental condition) and were repeated over LP2 (8 for each experimental condition) and trained test (16 for each experimental condition). F-S pair

assignments were randomized between participants. The order of F-S picture presentation was randomized within each LP1 and LP2 block.

Task design and procedure in healthy participants (Experiment 1). Participants performed a modified version of an associative inference task (e.g., (Zeithamova et al., 2012) (**Figure 11A**). The task consisted of two separate learning phases, Learning Phase 1 (LP1) and Learning Phase 2 (LP2), followed by a Testing Phase. In each of the acquisition phases, participants were requested to learn Face (F) – Scene (S) associations through feedback. Unbeknownst to the participants, in LP1 F-S associations were organized into eight picture subsets, each including two F-S pairs. Subsets in the associative condition involved one face image (F1) and two different scene images (S1 and S2). During learning, F1 was presented separately from S1 and S2, thereby promoting inferential learning between S1 and S2 through associative overlap. Picture subsets in the semantic condition involved two different face images (F1 and F2) and two different scene images (S1 and S2) from the same semantic category. Specific F-S pairs in the semantic condition were randomly assigned before the experiment started. LP1 was structured into 8 blocks, each including 32 trials in total (16 trials per experimental condition). LP1 was followed by LP2, which consisted of 16 different F-S pairs presented 8 times throughout the 8 blocks. Importantly, in LP2 all face images were novel but each of them was paired with a scene image from a different subset of pictures presented in LP1. Thus, 8 faces were associated with 8 scenes from each of the associative condition subsets (henceforth, associative condition in LP2) and 8 faces were presented with 8 scenes from each of the schematic condition subsets (semantic condition in LP2, thereby providing opportunities for integrative encoding of picture subsets from LP1 that had differential relational structure (i.e., associative or schematic)).

The structure of the trials was similar in LP1 and LP2. Each trial consisted of the presentation of a face at the top of the screen and two scenes at the bottom for 3500 ms. Participants had to wait for the appearance of the message 'RESPONSE' and they then had 1000 ms to indicate, by pressing a button, which of the two scenes was associated with the face. Following participants' choices, a delay period (grey background) of 500 ms preceded the feedback, which consisted of the presentation of a green tick (right choice) or a red X (wrong choice), each of which remained on the centre of the screen for 1000 ms. The appearance of the scenes on the right or left side of the screen was counterbalanced through the presentations. Additionally, in order to avoid stimulus-response learning strategies, every scene was shown as a correct choice for a particular face and as an incorrect choice when appearing with other faces, with the restriction that it could not appear twice as an incorrect choice with the same face. Therefore, the correct scene for a given face was always the same, but the incorrect scene was variable.

Two separate surprise forced-choice tests followed LP2: the generalization and the trained test. In the generalization test, participants had to indicate which of two faces seen during LP1 was associated with a face from LP2 presented at the top of the screen, thereby assessing inferential learning. This test consisted of 16 trials (8 for each experimental condition). In the trained test, two scene images appeared, and participants had to indicate which had been associated with the face image presented at the top of the screen. This test always followed the generalization test, thereby ruling out the possibility that accuracy in the inferential test could be explained by other factors (i.e., memory recall for pair associates) other than neural mechanisms elicited during LP2. In this test, all trained pairs from LP1 and LP2 were tested. In the generalization and direct test, the incorrect choice elements were all previously learned items that had been studied during the task. Pictures remained on screen until the participants responded, and there was no feedback informing the participants of the result of their choice. Test trials were separated by an inter-trial time randomized between 750 and 1250 ms.

Task design and procedure in TLE patients and healthy controls (Experiment 2). A shorter version of the experiment 1 task was implemented in TLE patients and control samples. More concretely, LP1 consisted of 12 subsets of F-S associations: 6 from the associative condition and 6 from the schematic condition. All pairs were presented 8 times throughout 8 different blocks. LP2 consisted of 6 face-context associations (3 from the associative condition and 3 from the schematic condition). At the end of the task, a generalization test consisting of 6 possible face-face associations, and a trained test consisting of 12 possible face-context associations were implemented.

Behavioural analysis. Participants' correct responses throughout LP1 and LP2 were calculated and averaged for each block of trials. A repeated-measures ANOVA including Block (8 levels) and experimental condition (associative and schematic) as within-subject factors was used for statistical assessment. Participants' accuracy in the tests was assessed by the proportion of correct choices separately for the generalization test and the trained test. Statistical significance was set at an alpha of 0.05. Greenhouse-Geisser epsilon correction was used to correct for possible violations of the sphericity assumption for statistical analysis when necessary; the adjusted p-values after the correction were reported.

EEG recordings and preprocessing in Experiment 1. EEG was recorded at a 500 Hz sampling rate (High-pass filter 0.01Hz, notch filter at 50Hz) from the scalp using a BrainAmp amplifier and tin electrodes mounted on an electrocap (Electro-Cap International) located at 29 standard positions (Fp1/2, Fz, F7/8, F3/4, FCz, FC1/2, FC5/6, Cz, C3/4, T3/4, Cp1/2, Cp5/6, Pz, P3/4, T5/6, PO1/2, Oz) and at the left and right mastoids. An electrode placed at the lateral outer canthus of the right

eye served as an online reference. EEG was re-referenced offline to the linked mastoids. Vertical eye movements were monitored with an electrode at the infraorbital ridge of the right eye (EOG channel). Electrode impedances were kept below 3 kΩ. EEG was band-pass filtered offline at 0.1 - 40Hz. Independent Component was applied to the continuous EEG data to remove blinks and eye movement artefacts. Trials exceeding ± 100 μV in both EEG and EOG within a -100 to 2500 ms time window from stimulus onset were rejected offline and not used in the time-frequency and neural similarity analysis detailed below. 7 participants were excluded from subsequent EEG analyses as they did not produce at least 5 artefact-free trials for each of the 8 learning blocks in LP2.

Time-frequency (TF) analysis. TF was performed using six-cycle complex Morlet wavelets in 7100 ms EEG epochs (2100 ms before stimulus onset through 5000 ms after) from LP2. Changes in time-varying energy (square of the convolution between wavelet and signal) in the 2-14 Hz band were computed for each trial and averaged separately for each experimental condition at the individual level. Before performing an overall average, power activity changes were computed with respect to the baseline of each participant (-200 to 0 ms from picture onset).

Similarity analysis. This analysis was set to assess for the possibility that the encoding of LP2 picture pairs elicited the reactivation of neural patterns triggered by picture pairs from the same memory network acquired in LP1, thereby suggesting, according to previous reports investigating inferential learning (Zeithamova et al., 2012), that neural reactivation arises as a mechanism supporting integrative encoding during LP2. To address this issue, we implemented a time-resolved trial-to-trial similarity analysis between EEG patterns elicited during the last block in LP1 and EEG patterns elicited throughout LP2. We reasoned that including trials only from the last LP1 block guaranteed that neural patterns taken in the analysis were the strongest and most stable memory traces associated with each picture pair in LP1, as learning accuracy in that block was almost perfect and similar between experimental conditions (see results below).

The similarity analysis was performed at the individual level, and included spatial (i.e., scalp voltages from all the 29 electrodes) and temporal features, which were selected in steps of 10 sample points (20 ms) of the resulting z-transformed EEG single-trials. Similarity analysis was implemented at single-trial level by correlating point-to-point the spatial EEG features throughout 2500 ms from picture onset. The similarity analysis was calculated using Pearson correlation coefficients, which are insensitive to the absolute amplitude and variance of the EEG response. R values were then Fischer z scored before statistical comparison analysis.

Cluster statistics of the EEG data. To assess for power differences between conditions at the temporal domain, we used a paired sample permutation test (Groppe, Urbach & Kutas, 2011) to deal with the multiple comparisons problem given the multiple sample points included in the analysis. This test uses the "*t* max" method to adjust the p-values of each variable for multiple comparisons (Blair and Karniski, 1993). Like Bonferroni correction, this method adjusts p-values in a way that controls for the family-wise error rate.

To account for scalp distribution differences (i.e., spatial dimension) between associative and schematic conditions in time-frequency data and to account for differences between conditions in the similarity analysis (i.e., temporal dimension), a cluster-based permutation test was used (Maris & Oostenveld, 2007), which identifies clusters of significant points in the resulting 2D matrix in a data-driven manner and addresses the multiple-comparison problem by employing a nonparametric statistical method based on cluster-level randomization testing to control for the family-wise error rate. Statistics were computed for each time point, and the time points whose statistical values were larger than a threshold ($p < 0.05$, two-tail) were selected and clustered into connected sets on the basis of x, y adjacency in the 2D matrix (defined by at least 2 contiguous points). The observed cluster-level statistics were calculated by taking the sum of the statistical values within a cluster. Then, condition labels were permuted 1000 times to simulate the null hypothesis, and the maximum cluster statistic was chosen to construct a distribution of the cluster-level statistics under the null hypothesis. The nonparametric statistical test was obtained by calculating the proportion of randomized test statistics that exceeded the observed cluster-level statistics.

3.3 Results

Experiment 1 (Healthy participants)

Behavioural performance. All participants were able to learn face-scene associations from the associative and schematic conditions in LP1 (**Figure 12A**). This was reflected by high accuracy (i.e., > 90%) in the participants' ability to choose the association pair correctly in the two conditions in the last block of the encoding paired t-test: $t(39) = 1.50$; $p = 0.14$). A repeated-measures ANOVA including condition (associative and schematic) and block (from one to eight) as within-subject factors confirmed accuracy improvement over the course of the task for all subsets of pictures (main effect of block: $F(4.03,157.22) = 174.96$, $p < 0.01$). However, that increment was less steep in the schematic than in the associative condition (Condition x block effect: $F(5.01,195.47) = 2.51$, $p = 0.03$).

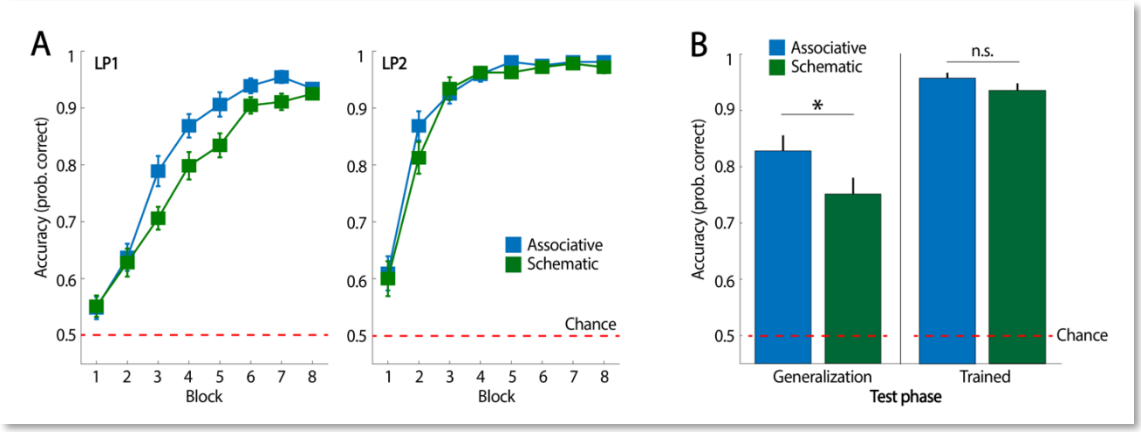


Figure 12. Behavioural data in healthy young participants (Experiment 1). (A) Averaged participants' accuracy in selecting the correct scene association with a given face throughout LP1 and LP2 for each experimental condition. **(B)** Averaged participants' accuracy in the generalization and the trained memory tests. *p < 0.05 and n.s., p > 0.05. Error bars indicate standard error of the mean.

In LP2, participants reached high levels of accuracy relatively rapidly and they were highly accurate (i.e., > 90%) in selecting the correct association by the end of the learning phase (**Figure 12A**). A repeated-measures ANOVA, including experimental condition and block as within-subject factors, revealed no significant differences between conditions ($F(1,39) = 2.56$, $p = 0.12$) or experimental condition x block ($F(7,273) = 0.78$, $p = 0.60$). A trend towards significance was found for the block factor ($F(5.20,202.99) = 1.87$, $p = 0.1$), indicating that participants' learning occurred very rapidly during encoding and reached a ceiling effect at early stages of the encoding rounds.

Participants showed, overall, high accuracy in the generalization test, thereby demonstrating that they had successfully integrated picture sets from LP1 during LP2 (**Figure 12B**). However, we found that accuracy was greater in the associative (Mean = 82.81%, SD = 17.15%) than the schematic condition (Mean = 75%, SD = 18.95%) ($t(39) = 2.48$, $p = 0.018$). Importantly, participants were highly accurate in the trained test (i.e., > 80%) and their performance did not differ between differ between conditions ($t(39) = 1.36$, $p = 0.18$) (**Figure 12B**), thereby confirming that they retained the trained associations from the two experimental conditions in equal measure. Altogether, the behavioural findings suggest that the underlying structure of the associations learned during LP1 may have had an impact during encoding strategies in LP2, which is when participants had the possibility to create the relational links needed to establish inferential learning between face-scene pairs.

Theta oscillations. To test our hypothesis that theta oscillations would persist longer in time in response to schematic than associative conditions, we performed a time-resolved comparison of theta power changes elicited during the 2500 ms after stimulus onset between associative and schematic conditions. We targeted a broad frequency range of theta oscillations spanning 3 - 6 Hz, which is a slightly lower frequency than the traditional theta band according to recent reports (Jacobs et al., 2013; Watrous et al., 2013), and to scalp electrophysiological findings using similar experimental designs (Backus et al., 2016; Sans-Dublanc et al., 2017). In line with this literature, theta power changes at this frequency range were pronounced during LP2 associative and schematic condition trials (**Figure 13**). Importantly, and confirming our hypothesis, we found that the theta power increase was more extended in time in response to picture pairs that were linked to schematic rather than to associative memory structures acquired in LP1 (**Figure 13**). A cluster-based permutation test revealed that the persistent theta power increase in the schematic condition as compared to the associative condition was distributed over the scalp, spanning frontal, central, and posterior scalp sensors (**Figure 13**).

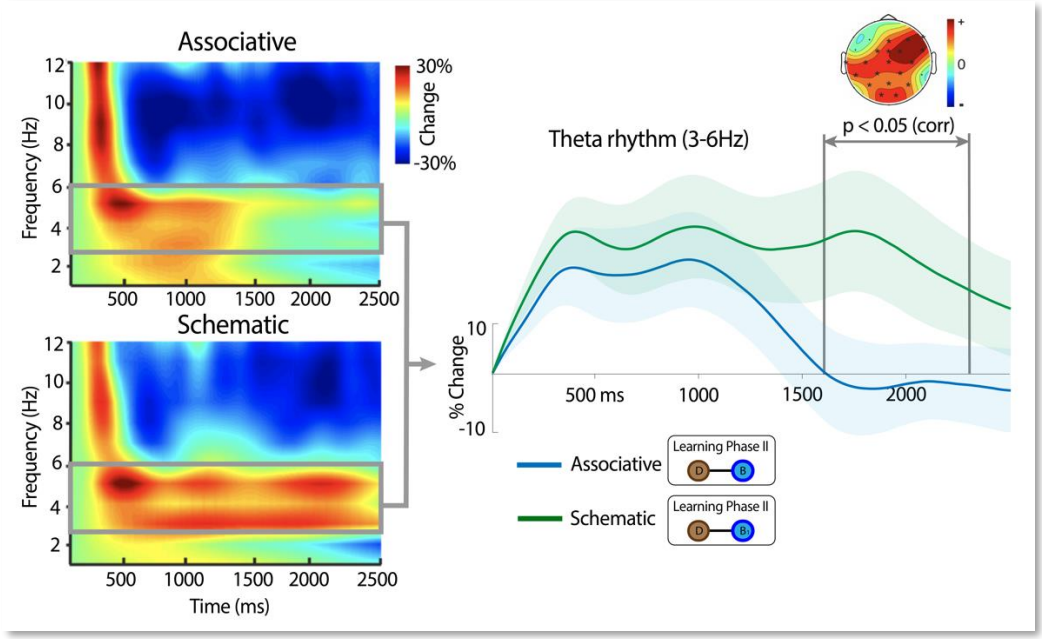


Figure 13. Theta oscillations in LP2. Group-averaged changes in spectral power (averaged over all scalp sensors) elicited by picture pairs from the associative and schematic conditions in LP2. A power increase in the theta band was observed in both conditions. However, that power increase lasted longer during the encoding of picture pairs from the schematic than the associative condition. Statistical time window differences between conditions are indicated with bars (point-to-point paired t-test threshold $p < 0.05$). Significant time points corrected for multiple comparison were between 1730 and 1950 ($p < 0.05$; one-tail) within that time window. Spatially distributed theta differences between schematic and associative conditions are also depicted; sensors that were significant and corrected for multiple comparisons at cluster level are marked with a black asterisk. Thick theta line represents the mean across participants and point-to-point standard error is depicted in shaded colour.

Neural similarity. This analysis revealed that the patterns of EEG responses elicited by picture pairs in the last LP1 block correlated with EEG patterns elicited during the encoding of different picture pairs that overlapped in content (**Figure 14A**). However, the degree of neural similarity differed between experimental conditions. More specifically, picture pairs linked to learned picture pairs in LP1 from the associative condition showed significantly stronger neural similarity values over a window of ~500 to 2000 ms from stimulus onset in LP2. On the other hand, EEG patterns elicited by picture pairs in the schematic condition showed an increased neural similarity earlier in time during the encoding of linked LP2 picture pairs (at around 300-500 ms from LP2 picture onset) (**Figure 14B**). In addition, the same analysis of LP1 trials from the first block during learning did not show any statistically significant differences between trial conditions, thereby suggesting that the similarity effects were greatest when neural patterns reflected robust memory representations of network representations at the end of LP1 (e.g., **Figure 11D**).

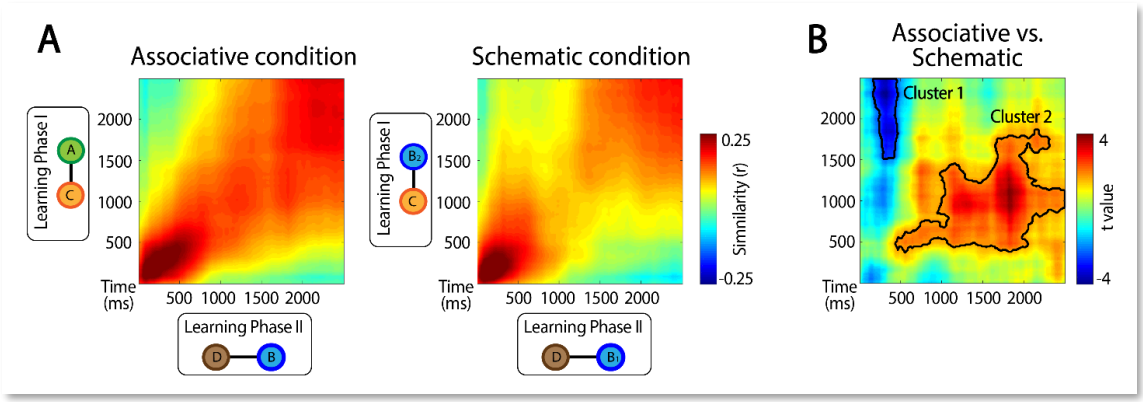


Figure 14. Neural pattern similarity between events that overlapped within memory network structures in the task. **(A)** Group-averaged time-resolved degree of similarity between C-A and C-B1 events from the last block of trials in LP1 and the corresponding D-B trials during LP2. Neural similarity in this analysis offers a measure of how similar two neural patterns are when elicited by events which, although separated in time, share partial memory information in the current task. **(B)** Point-to-point t value map from comparing schematic and associative neural similarity results. Two clusters of statistically significant similarity values were found ($p < 0.05$, cluster-based permutation test) (indicated by a thick black line).

Experiment 2 (TLE patients and matched controls)

In line with experiment 1, a mixed-design ANOVA, including condition and block as a within-subject factor and group (TLE and control) as a between factor in LP1 data, revealed a statistically significant main effect in condition ($F(1,26) = 5.14$, $p = 0.03$) and block ($F(7,182) = 19.35$, $p < 0.01$), and a non-significant condition x block interaction ($F(7,182) = 1.37$, $p = 0.22$), which indicates that TLE patients and controls successfully encoded picture pairs over the task but that events from

the associative condition were learned faster. No significant differences were found between groups in any of the contrasts (i.e., condition x group: F (1, 26) = 0.6, p = 0.44, block x group: F (7,182) = 1.66, p = 0.12; and condition x block x group: F (7,182) = 2.03, p = 0.053). The same statistical analysis of behavioural data from LP2 revealed that both groups successfully acquired picture pairs over the course of the task (block effect: F(4.13,107.37) = 15.64, p < 0.01; block x group interaction: F(7,182) = 0.80, p = 0.58), independently of the experimental conditions (condition effect: F (1,26) = 0.03, p = 0.87; condition x group interaction: F(1,26) = 1.11, p = 0.30); condition x block x group: F(7,182) = 0.95, p = 0.47 (**Figure 15 A**).

We next assessed for group differences in the generalization and trained test through an ANOVA, including test type (trained and generalization), condition (Associative and Schematic) as within-subject factors and group (TLE and control) as a between-factor factor. This analysis revealed a statistically significant main effect of group (F(1,26) = 11.37, p < 0.01) and a group x test type x condition effect (1,26) = 4.74, p = 0.03) but not any other statistically significant x group interaction effect (test type x group: F(1,26) = 2.42, p = 0.13; condition x group: F(1,26) < 0.1, p = 0.89), thereby indicating the TLE and controls' response accuracy differed as a function of test type and condition. To try to identify the source of this triple interaction, we first searched for group differences in the generalization test through another ANOVA, including condition and group as a within- and between-subject factors, respectively. This analysis revealed a significant main effect of group (F (1, 26) = 9.22, p = 0.005) but not of condition (F (1, 26) = 0.59, p = 0.45), nor a condition x group interaction (F (1, 26) = 1.30, p = 0.26) (**Figure 15 B**), thereby indicating that TLE patients showed poorer ability to generalize in the associative and schematic condition. In fact, while behavioural accuracy in each of the conditions was high and above chance in healthy controls (Associative: t(13) = 6.87; p < 0.01; Schematic: t(13) = 2.57; p = 0.02), TLE patients performed at chance in the tests (Associative: t(13) = 0.31; p = 0.76; Schematic: t(13) = 0.30; p = 0.76). A paired-sample *t*-test analysis showed that accuracy did not differ statistically between conditions at within group level (controls: t (13) = 1.82, p = 0.09; TLE patients: t (13) < 0.5).

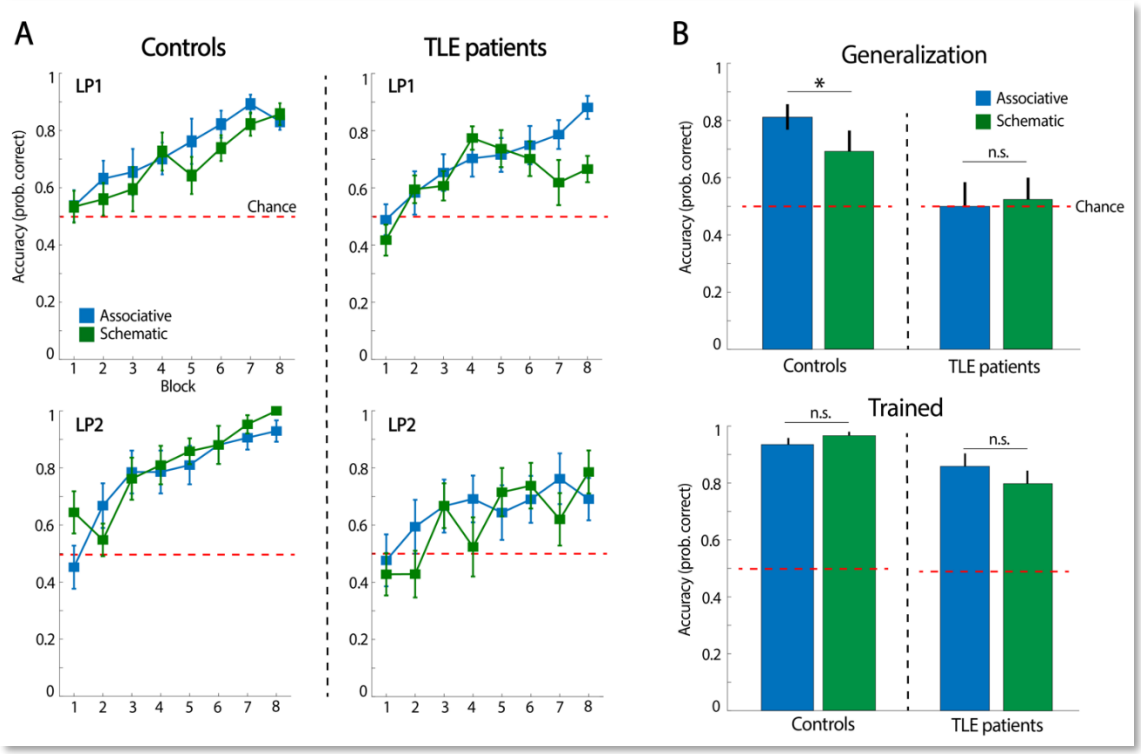


Figure 15. Behavioural data in TLE and healthy control participants (Experiment 2). **(A)** Averaged participants' accuracy in selecting the correct scene association with a given face throughout LP1 and LP2 for each experimental condition. **(B)** Averaged participants' accuracy in the generalization and trained memory tests. *p < 0.05 and n.s., p > 0.05. Error bars indicate standard error of the mean.

We then repeated the same ANOVA strategy regarding memory accuracy for trained events. An ANOVA including condition and group as a within- and between-subject factors, respectively, showed a significant group ($F(1, 26) = 13.61$, $p < 0.01$) but not a group x condition interaction effect ($F(1, 26) = 2.13$, $p = 0.16$), indicating that TLE patients were less accurate in recognising the individual face-scene associations acquired during LP2 when compared to controls (**Figure 15B**). Importantly, both controls and TLE patients showed consistent above-chance performance in each of the test measures (controls – associative condition: $t(13) = 14.14$; $p < 0.01$; controls – schematic: $t(13) = 20.21$; $p < 0.01$; TLE patients – associative: $t(13) = 1.94$; $p = 0.07$; TLE patients – schematic: $t(13) = 5.1$; $p < 0.01$). A paired-sample *t*-test analysis showed that accuracy did not differ statistically between conditions at within-group level (controls: $t(13) = -0.56$, $p = 0.58$; TLE patients: $t(13) = -1.33$, $p = 0.21$).

3.4 Discussion

A challenge in memory research has been to understand how structures of knowledge can aid integrative encoding of new information. Here, we showed that the process is hippocampus-

dependent, as TLE patients were impaired in inferring novel relations between elements within mnemonic networks but not in retrieving individual pictures. In addition, we observed more persistent and widespread theta activity (3-6 Hz) in the scalp during the encoding of novel pictures related to schematic memory networks, suggesting that theta may reflect distances between elements within an arbitrary representational network space. Finally, we found high similarity values for neural activity patterns elicited by novel and related events only within associative networks, thereby suggesting that neural reactivation may be important in integrative encoding only when novel information relates to a mnemonic network of elements linked by direct associations.

Our findings provide evidence that MTL structures, including the hippocampus, are essential to enabling the rapid integration of new information within stored knowledge in a schematic structure. These results align well with previous studies that revealed the critical role of the hippocampus in enabling inferential learning between different episodic events that overlap in the perceptual content in healthy individuals (Schlichting and Preston 2015; Zeithamova et al., 2012); and in patients with lesions in the MTL (Pajkert et al., 2017). However, the current findings extend these findings by showing that the hippocampus-dependent nature of this process also affects inferential learning that relies on relational links between distinct episodes whose overlapping content is at the conceptual level (i.e., stimulus category). In fact, the notion that the hippocampus is critical in encoding new experiences into congruent schematic memories has received support from animal (Tse et al., 2007, 2011) and human studies (Schlichting & Preston, 2015; Van Kesteren et al., 2010). Interestingly, the degree to which hippocampal integration mechanisms identified in episodic inference contribute to other forms of generalization, such as concept learning, has often been neglected in the literature. However, recent fMRI findings in humans showed that the anterior hippocampus, in concert with the PFC, generated and tracked the prototype representation of multiple items that overlapped in their content, and the degree to which participants relied on such conceptual representation abstracted across the training set predicted their ability to generalize in a later test (Bowman & Zeithamova, 2018).

The notion that prior knowledge, and schema representations in particular, has an impact in memory has been long observed in psychological research (e.g., Bartlett, 1932; Craik & Lockhart, 1972). However, the investigation of how schemas influence memory formation has suffered from the heterogeneous usage of the term in neuroscience. In the current study, we labelled schematic memory to a set of complex interrelated picture association network that deemed to incorporate many of the necessary features that are thought to qualitatively differ from a purely associative memory network (Ghosh & Gilboa, 2014). Indeed, here, schematic memory networks are defined

by an associative network structure, that emerged based on multiple episodic exposure, that relayed on representational units that lack of a unit detail (i.e., their elements are interrelated via semantic concepts), that are adaptable, as they allow the integration of new elements, and that are organized hierarchically. Although we believe these network properties deemed for a qualitative difference with purely associative memory networks, arguably, some of them lacked a full empirical assessment in our experimental design. For example, while the notion that a semantic concept brings hierarchy into a memory network is well established in psychological models of memory representation (e.g., Collins & Quillian, 1969), it would be important to determine the extent to which participants activate purely conceptual memory representation during learning in our experiment. In the same line of argumentation, it would be important to determine the extent to which the decrease in generalization performance seen in the schematic condition cannot be, at least partially, attributed to an increase of interference driven by the need to integrate more associations in schematic than in associative memory networks. Undoubtedly, the study of reaction time patterns in participants' responses during learning would have helped inform about this possibility (i.e., longer RTs to trials from schematic than from associative condition in LP2). However, to exclude that possible differences between conditions in the temporal evolution of specific neural responses recorded from scalp EEG recordings could be attributed artefactual signals derived from motor preparation and response, participants were required refraining participants to response within the temporal window of interest (i.e., while encoded pictures were present in the screen during 3 seconds).

Importantly, we observed that the learning-eliciting theta oscillations during the integration of novel information into an existing memory network may reflected its underlying organizational properties. Specifically, we found that theta activity persisted longer when new information was linked to schematic memory networks than when novel items had to be integrated into memory networks with an associative structure. These findings suggest that theta oscillations are a putative neural mechanism by which our brain searches for memories throughout the representational space. Indeed, a plethora of animal (Buzsáki, 2002; Buzsáki, Lai-Wo & Vanderwolf, 1983) and human studies have revealed the relevant role of theta oscillations in supporting spatial memory and navigation (Ekstrom et al., 2005; Jacobs et al., 2013). Several recent studies have suggested that theta power may itself correlate with spatial distances (Bush et al., 2017; Vass et al., 2016). Intriguingly, a recent study using deep electrodes in the hippocampus of human epileptic patients showed that theta activity coded semantic distances between words from a list (Solomon et al., 2019), thereby lending support to the notion that theta oscillations reflect relations between nonspatial items in memory. Our findings that theta elicited a greater response from events related to schematic memory networks than those related to

associative networks contribute to the idea that theta oscillations may signal memory trajectories in the representational space. These findings contribute to the idea that theta oscillations may signal memory trajectories in a general-domain representational space.

Prior literature has emphasized how inferential learning relies on mechanisms of memory reactivation (e.g., Zeithamova et al., 2012). These studies revealed that prior event details are reinstated at the encoding of related experiences and that this supports participants' ability to infer relationships between distinct events that share content. The current study builds upon and significantly extends prior studies by showing that the representational nature and temporal dynamics of such reactivation during inferential encoding depend on the organizational structure of the related memory network. Indeed, our representational similarity analysis revealed high correlation between EEG patterns elicited by events encoded in LP2 and EEG patterns triggered by related events from the previous LP1 phase. However, while we found a similarity increase in a large cluster of time points, from ~500 to 2500 ms stimulus onset, between EEG-elicited patterns with new and related events within the associative network, neural similarity between new events and events within the related schematic network was only higher for a brief window of time. This differential pattern of similarity results suggests that the reactivation nature of prior memory events during integrative encoding may adapt as a function of the structural properties of the related memory network. Accordingly, only novel events that largely overlap in content with episodic content from an associative memory network would entail a detailed reactivation of the related event. We reasoned that such an adaptive property of the memory systems would be optimal in our daily life activity, as most of our experienced events ultimately share a relationship with stored memories. We conjecture that an efficient regulatory mechanism may exist to avoid the costs of inducing memory reactivation of specific memories during the ongoing encoding, while maximizing the benefits of maintaining a linked memory representation of an encoded event with previously stored memory representations. We speculate that this regulatory mechanism may be guided by the ability of a reminder/cue to navigate throughout the representational memory space and rapidly find associated events. If they are found, then these memory representations are reactivated and integrated in a common representational space (i.e., associative network in the current experiment). However, when a given cue does not match a specific representation for an event, then it moves to higher levels of representation, such as the conceptual level, thereby maximizing the ability to keep the current encoded event related to other memories that overlap at this representational level, as in the schematic network condition in the present experiment. Intriguingly, the pattern of similarity results that we obtained in the schematic condition fit recent EEG findings in humans revealing that information flow during encoding and retrieval may be reversed in order (Linde-Domingo et al., 2019). Thus, while visual

encoding starts with low-level perceptual followed by high-level abstract processing, the mnemonic stream can prioritize the access to conceptual information. Our finding that the EEG patterns from early temporal windows elicited by novel events were similar to EEG patterns elicited at a late temporal window by the related event within a schematic memory network suggests that a similar retrieval-oriented prioritization to access conceptual information may be engaged in the schematic condition in our study.

Taken together, our findings shed light on the neural mechanisms that support the integration of novel information into existing memory networks. Our central finding is that both associative and schematic structures of memory networks aid integrative encoding of new information via the hippocampus, but that they engage different theta and neural reactivation patterns. Theta oscillatory activity was more persistent and widespread when the encoded event was to be integrated into a schematic memory network, lending support to the notion that theta oscillations may reflect distances between elements within representational network space. On the other hand, a stronger and temporally extended reactivation of prior event memories was found only during the encoding of events that were integrated into associative memory networks, thereby suggesting the existence of regulatory mechanisms that promote the reactivation of related memory events when they belong to an associative structure in which multiple events are linked by direct association within a network. More broadly, the results emphasize the flexible nature of memory, whereby novel experiences and organizational properties of stored knowledge interact to enable structured representation of information in an ever-changing environment.

Table 1. Individual patient characteristics.

Diagnosis	Gender	Age	IQ	Years Educ.	Years since onset	Clinical notes / aetiology	Treatment
R-MTL	M	53	100	20	12	Arterio-venous malformation	Carbamazepine 600 mg/day Brivaracetam 150 mg/day
R-MTL	F	52	80	12	15	Cavernoma	Lacosamide 250 mg/day
L-MTL	M	26	80	8	12	Encephalocele	Escicarbazepine 160 mg/day Perampanel 8 mg/day Clobazam 20 mg/day
R-MTL	F	46	90	8	9	PET hypometabolism	Lacosamide 200 mg/day Levetiracetam 3000 mg/day Eslicarbazepine 1200 mg/day
R-MTL	F	38	137.5	17	6	Amygdalar dysplasia	Duloxetine 90 mg/day Eslicarbazepine 800 mg/day Levetiracetam 500 mg/day Lacosamide 150 mg/day Clobazam 10 mg/day
L-MTL	M	43	95	12	30	Parieto-temporal gliosis	Eslicarbazepine 400 mg/day Pregabaline 225 mg/day
L-MTL	F	70	80	8	28	PET hypometabolism	Carbamazepine 400 mg/day Clobazam 15 mg/day
R-MTL	M	56	110	13	43	Hippocampal sclerosis	Topiramate 100 mg/day Eslicarbazepine 1600 mg/day Levetiracetam 200 mg/day Perampanel 8 mg/day
L-MTL	M	35	90	21	5	PET hypometabolism	Eslicarbazepine 1600 mg/day Zonisamide 500 mg/day Perampanel 2 mg/day
L-MTL	F	57	100	12	13	Hippocampal sclerosis	Escitalopram 10 mg/day Lamotrigine 400 mg/day Clobazam 5 mg/day
R-MTL	F	26	110	21	3	PET hypometabolism	Perampanel 4 mg/day Levetiracetam 300 mg/day
L-MTL	M	51	90	8	29	Hippocampal sclerosis	Phenobarbital 100 mg/day Levetiracetam 3000 mg/day Eslicarbazepine 1600 mg/day
R-MTL	M	57	80	7	49	Hippocampal sclerosis	Carbamazepine 600 mg/day Levetiracetam 4000 mg/day Zonisamide 300 mg/day
R-MTL	M	53	95	20	13	Arterio-venous malformation	Carbamazepine 600 mg/day Brivaracetam 150 mg/day

Chapter 4

Study 2

This study corresponds to:

Nicolás, B., Wu, X., Dimiccolli, M., Sierpowska, J., Saiz-Masvidal, C., Soriano-Más, C., Radeva, P., Fuentemilla, L., Neurophysiological signatures of the retrieval of individual autobiographical memories for real-life episodic events (2020).

Chapter 4: Study 2

Neurophysiological signatures of the retrieval of individual autobiographical memories for real–life episodic events

Autobiographical memory (AM) refers to recollected events that belong to an individual's past. In a classical episodic retrieval experiment in a laboratory, the events to be remembered are words or pictures that have hardly any personal relevance. While such stimuli provide necessary experimental and controlled conditions helping to advance in the understanding of memory, they do not capture the whole complexity of real-world stimuli. Recently, the incorporation of wearable cameras has allowed us to study the cognitive and neural bases of AM retrieval without active participant involvement, and they have been demonstrated to elicit a strong sense of first-person episodic recollection enhancing ecological validity. Here, we provide a new approach to understanding the retrieval of personal events, implementing a convolution network-based algorithm for the selection of the stimuli while monitoring participants' memory retrieval with scalp EEG recordings over three periods of time after encoding (1 week, 2 weeks, and 6 to 12 months). We also examined an individual with a condition termed Aphantasia that provided more insights into the sensitivity of our protocol in the investigation of individual AM using real-life sequences.

4.1 Introduction

Autobiographical memories (AMs) are specific individualized compilations of our personal past daily life episodic experience. The ability to recollect detailed information about past autobiographical events is a hallmark of episodic memory (Tulving, 2002). However, the vast majority of behavioral and neuroimaging studies of episodic retrieval have used laboratory encoded stimuli, such as words or pictures, as memory probes. While such stimuli provide researchers with tight experimental control over the perceptual qualities, exposure duration, and retention interval of the events being tested, laboratory stimuli lack the richness of most real-world experiences (Chow & Rissman, 2017; Chow et al., 2018; Diamond & Levine, 2020; Nielson et al., 2015; St. Jacques et al., 2011). Thus, it is not unsurprising that performance on standard laboratory-based memory tasks may be largely unrelated to one's autobiographical retrieval abilities, as demonstrated by individuals with "highly superior autobiographical memory" (LePort et al., 2012; LePort et al., 2017; Patihis et al., 2013) and "severely deficient autobiographical memory" (Fuentemilla, et al., 2018; Palombo et al., 2015).

A hallmark in the advance of our understating of how episodic memory serves to retrieve real-life autobiographical experiences would be to have methods that allowed the automatic recording of daily life episodes prospectively at the individual level. Through such an approach, researchers would have the opportunity to examine an exhaustive collection of realistic real-life experience material of an individual ahead of sampling control during encoding. Previous research efforts proved effective in cueing AMs sampled at the individual level. Most notably, the use of self-recorded audiotapes or videos documenting selected real-life event experiences has helped characterize the involvement of a core brain network supporting the retrieval of AMs including the medial temporal lobe and the frontal and parietal regions (Levine et al., 2004; Svoboda & Levine, 2009), coordinated via neural oscillatory mechanisms in the range of the theta band (4-8Hz) (Fuentemilla et al., 2018). However, this approach requires individuals to actively record selected experiences during their daily life routine, and therefore the effectiveness of the retrieval cues may still be partially explained by additional processes engaged during encoding such as selection, organization, and rehearsal of the recorded material.

The recent incorporation of portable technology, such as wearable cameras, to study the cognitive and neural basis of AM retrieval appeared to be a promising venue for addressing the previous concern. This technology allows each individual to capture automatically (e.g., every 30 seconds) face-front sequence of pictures of daily life activity without the need for the participant to be actively engaged in the recording process. Though this is still in its infancy, researchers have already shown that the presentation of pictures acquired with a wearable camera engaged the

core AM retrieval network (Cabeza et al., 2004; Rissman et al., 2016) and elicited a strong sense of first-person retrieval in participants, even when they were confronted with others' pictures depicting the same content (St. Jacques et al., 2011). It proved suitable to test how the hippocampus encodes spatial and temporal properties of our real-life experiences (Nielson et al., 2015). However, given the unfolding nature of our experience, the continuous and automatic photographic process ends up yielding a large number of pictures that require researchers to review and organize them so that they can manually select those, among the large set, that will likely cue a strong sense of episodic recollection in each participant. The fact that only a subsample of pictures are used as retrieval cues in a memory test, and that they are selected based on the experimenter's criteria, challenges the notion that this approach, as it stands, may be suitable to address fundamental questions of episodic memory, such as "how do we remember or forget single real-life episodes from our past?" and "how do we retrieve individual event episodes over time?"

In the current study, we sought to overcome these issues by recording electroencephalographic activity (EEG) while healthy participants retrieved their own AMs cued by pictures taken automatically (i.e., every 30 seconds) by a wearable camera during one week of daily life routine. To ensure pictures presented during the test cued most of the individual experiences that unfolded during the encoding week, we implemented a convolutional network-based algorithm (SR-clustering, Dimiccoli et al., 2015) on the entire recorded picture set that automatically grouped together temporally adjacent images sharing contextual and semantic attributes, akin to how we conceive what underlies an event episode from a perception and memory perspective (Zacks & Swallow, 2007), which has been recently shown to be a fruitful strategy to catalogue ecologically valid episodic memories (Jeunehomme & D'Argembeau, 2018, 2019). In doing so, the large picture set collected reflecting an entire day's life activity (e.g., ~400 pictures) is grouped into a workable number of picture subsets (e.g., ~20) depicting sequences of temporally adjacent episodic events (e.g., breakfast at home, commuting to work, meeting with office colleagues, lunch, etc.). Thus, we reasoned that by picking a representative picture from each of the subsets, it would then be possible to investigate whether an individual is capable of recollecting detailed information about the entire set of past experienced events. To assess how the passing of time impacted on the retrieval process of an event episode, we asked each participant to recollect their episodes one week, two weeks, and 6 to 12 months after the encoding period. Additionally, participants were asked to enroll in a separate study that required them to encode and retrieve, one week after the fact, pictures depicting indoor and outdoor scenes. This task, akin to standard lab-based experimental scenarios commonly used in memory research, was thought to help

delineate differences between retrieval processes for when participants' memory was cued by real-life autobiographical vs. lab-based event experiences.

Complementing the behavioral data, we also aimed to analyze well-known neural response activity widely studied in the context of episodic memory retrieval, such as Event-Related Potentials (ERPs) Old/New effects (Friedman & Johnson, 2000) and neural oscillations in the theta range (4-8Hz) (Nyhus & Curran, 2010). More concretely, we expected to identify cued-locked distributed ERP positive responses associated with the successful retrieval of real-life episodic events (Wilding, 1999) and cue-locked modulation of EEG oscillatory activity specifically of the theta band upon successful retrieval. These two neural indexes may well show a distinctive pattern of response as a function of passing of time and lab-based vs. real-life contexts, thereby helping refine the neural underpinnings that underly the retrieval of recent vs. remote autobiographical memories for routine everyday life experiences.

Finally, AM for everyday life activity was examined in an identified a person with confirmed Aphantasia (Zeman et al., 2015; Zeman et al., 2010) using the same wearable camera experimental protocol described previously. GB, as it has been previously described in similar examples (Keogh & Pearson, 2018), was an individual that showed a specific lack of visual imagination while preserving the rest of the cognitive abilities intact. Visual imagination is critical in determining the retrieval of high-quality episodic memories (Greenberg & Rubin, 2003) and it has been suggested as a feature to help distinguish individuals in terms of their ability to recollect AMs (Palombo et al., 2018). Here, we aimed to use our novel wearable camera-based experimental design to characterize GB's AM and with that to gain insight into the sensitivity of our protocol to scrutinize AM at the single subject level.

4.2 Materials and methods

Participants

Sixteen healthy participants (8 females) participated in experiments 1 and 2. The range in age was 22-37 years old (average age=27.68 years old (SD=4.22)). All participants provided informed written consent for the protocol approved by the Ethics Committee of the University of Barcelona. Participants received financial compensation for their participation. Two of the participants could not complete the follow-up in experiment 1 (see details below) and these participants were excluded from all analyses.

In addition, we examined a person with Aphantasia, referred to as case GB (not actual initials). GB was a 40-year-old male who contacted our research group after reading an article about Aphantasia in popular media. He recognized his personal experience with the information described in the article. The Vividness of Visual Imagery Questionnaire (VVIQ) (Marks, 1973) confirmed that GB had Aphantasia as he scored 8 (z = - 5.72) on a scale of 0 (minimum or complete lack) to 224 (maximum) in the test. GB reported no neurological, ophthalmological, or psychiatric etiology of his reported lack of imagery. Neuropsychological results are described in supplementary Table 1. Structural MRI (see Methods for details) showed minor white matter high intensities and borderline fronto-temporal atrophy, both within the normal limits for his age. GB's MRI scan was compared to a control sample of six participants (males, average age = 30.83 years old (SD = 3.87), average education years = 14.50 (SD = 4.37)).

Experiment 1: Retrieval of real-life memories

Design overview

Participants were asked to come to the training session a few days before starting the study. They were informed about how the camera worked and they read, understood, and signed the informed consent. We took special care in providing details on privacy issues so that all participants were fully aware of them before the study began. In the current study, participants wore the wearable camera for a period of 5-7 consecutive days (mean = 6.64 days, SD = 0.63), including both week and weekend days. The data collection period was established from morning to evening (between 12-14 hours per day). Once participants finished data collection, they were requested to return the materials to be processed. Participants confirmed not having checked the pictures during the recording week. Participants returned to the lab to be tested one week later (T1), two weeks later (T2), and from 6 to 14 months after the last day of data collection (Follow-up, hereafter FU; mean = 10.87 months, SD = 2.02 months). See **Figure 16** for a summary of the experimental design.

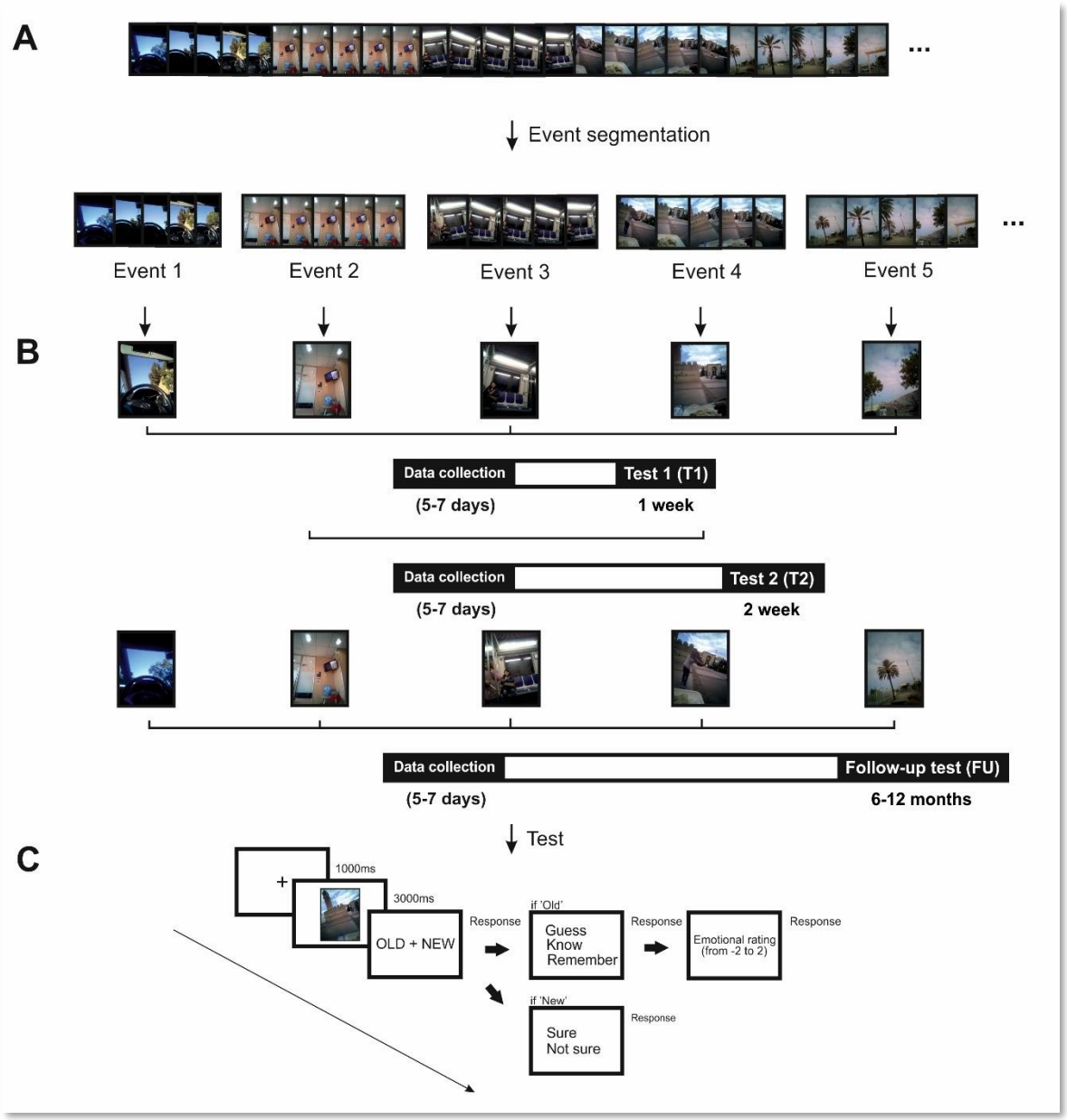


Figure 16. (A) Event segmentation approach. Example of a stream of pictures obtained from one participant after one week of data collection. The implementation of the SR-Clustering algorithm allows the automatic organization of picture sequences into a set of meaningful events by the identification of similar context and semantic features. **(B) Experimental design.** One representative photo from each event sequence of pictures was selected and distributed to each of the three memory tests that followed the picture collection week. A recognition memory for the was implemented one week (T1), two weeks (T2) and from 6 to 12 months (Follow-up test (FU)) after the data collection. Events extracted from picture sequences were numbered consecutively and pictures related to even numbered events were used as memory cues in T1 test and odd numbered event pictures in T2 test. Different pictures from same events tested in T1 and T2 were selected as cues in FU test. **(C) Recognition memory task**. Pictures were presented on the screen for 3000 ms. Afterward, an 'Old/New' question appeared on the screen. If the pictures were seen as 'Old', a "Remember/Know/Guess" appeared on the screen. Next, participants were asked to rate their emotional response towards the event indicating whether was positive or negative on a scale ranged from 2 (maximum positive) to -2 (maximum negative) being 0 neutral emotion. If the picture was seen as 'New', 'Sure/Not sure' judgment appeared on the screen.

Wearable camera

We used the wearable Narrative clip 2 camera® (http://getnarrative.com/) with a camera sensor of 8MP and a resolution of 3264x2448(4:3). The camera was programmed to automatically take images every thirty seconds and produced pictures with an egocentric viewpoint. Participants were instructed to wear the device on a lanyard around the neck. Narrative clip 2 incorporated a downloading app that allowed participants to download the pictures directly to a hard drive. Participants were instructed to not watch the pictures until the experiment finalized. None of the participants reported having done so at the end of the study.

Picture selection

We implemented a deep neural network-based algorithm, SR-Clustering, to automatically organize the stream of each participant's pictures into a set of temporally evolving meaningful events (Dimiccoli et al., 2015). The algorithm segments picture sequences into discrete events (event segmentation; e.g., having breakfast in a kitchen, commuting to work, being in a meeting) on the basis of its ability to identify similar contextual and semantic features from the picture stream. See Figure 1A for the event-segmentation approach.

The implementation of the SR-Clustering algorithm provided a variable number of discrete events for each participant per day, and each event included 8 to 20 pictures. Each participant's events were then manually inspected and those which displayed non-meaningful episodes (e.g., all pictures were blurred, or when the camera was pointing to the roof or was blocked by clothes) were discarded from the study. Picture events that described interactions with participants' relatives were excluded from the study. Three independent experimenters rated and selected the set of event pictures for each participant on the basis of these criteria, and only those events that were consistently selected by the three raters were included in the final set of picture events in the study (average number of events across participants Mean = 322, SD = 127). Note that the consistency across experimenters was set to ensure that the events captured by the algorithm were meaningful and did not involve implementing a subjective inclusion/exclusion selection criterion to which events should be included later in the memory test by the experimenters. The variability observed in the number of events between participants reflected the diversity of each participant's daily life activities (e.g., a person working indoors for 8 hours results in fewer events compared with people working outdoors).

Once the images were organized into discrete events, we selected a representative picture from each event, thereby ensuring most of the past episodic experience was brought into the test. We then numbered the sequence of event pictures and assigned even-numbered pictures to be used as memory cues for test T1 and odd-numbered pictures to be included in the T2 test. FU included picture cues used in T1 and T2 in the same proportion. Pictures cues presented to one participant depicting her own past (Old) were also presented to another participant as New images. This ensured that differences between Old and New pictures presented to each participant were only based on the image's direct link to ones' past while preserving the rest of the characteristics intact during the test (e.g., angle of view, picture image features, description of routine daily life activities). See **Figure 16B** for a summary of the experimental design.

By design, none of the participants were friends with each other, and we never encountered an instance where two concurrently enrolled participants came into direct contact with one another while wearing their cameras.

Recognition memory task

In the test, pictures were presented on the screen for 3000 ms. Afterwards, when an "Old/New" question appeared on the screen, participants were required to judge whether the picture reflected an event from the participant's own daily life (Old) or was experimentally novel, signaling with the right index and middle fingers, respectively. Next, participants were asked to judge whether they were "Sure/Not sure" when indicated an image was "New" and "Remember/Know/Guess" when images were seen as "Old". Participants were instructed that "Guess" referred to when they had no contextual memory reference for what was depicted in the image, but they recognized the content as being from their own life (e.g., viewing ones' living room). "Know" was the signal for when the visual content in the picture was highly familiar but the subject could not determine what unfolded in it, perhaps because the event on the test was part of a routine (e.g.: playing football on Thursdays), while "Remember" was the signal for when the picture elicited a vivid memory of that specific event and it could be located in time. Participants' ability to order each event depicted in the pictures along the encoding week was tested afterward more concretely, when they were asked to indicate whether the pictures depicted an event that took place at the "beginning, middle or end" of the encoding week as the image appeared on the screen. Finally, participants were asked to rate the degree to which each of the pictures elicited an emotional response and to indicate whether it was positive or negative on a scale that ranged from 2 (maximum positive) to -2 (maximum negative), with 0 being neutral

emotionally. See **Figure 16C** for a summary of the recognition memory task. Temporal ratings are not shown in the design overview.

Experiment 2: Retrieval of lab-based memories

The experimental design was similar to experiment 1, but differed mainly in that images depicting real-life experiences were replaced by neutral images of indoor and outdoor scenes extracted from previous experiments (e.g., Bunzeck & Düzel, 2006; Fuentemilla et al., 2010). Thus, the design involved an encoding phase and a test phase administered after each participant finished the retrieval session from the FU condition in experiment 1.

In the encoding phase, participants were instructed to indicate whether scene pictures were indoor or outdoor images. There were 80 scenes (40 indoor and 40 outdoor, presented in random order). Each scene was presented for 2000 ms preceded by a 1500 ms fixation period and followed by the text "indoor/outdoor" that prompted participants' response (responding with the index or middle finger of their right hand). A period of 10 minutes of rest separated the study from the test phase.

In the test phase, a scene picture was presented on the screen for 3000 ms. Afterwards, when an "Old/New" question appeared on the screen, participants were required to judge whether the word was presented in the previous study phase (Old) or was experimentally novel (New) with the right index and middle finger, respectively. The test phase included 160 scene images in total (80 Old and 80 New, randomly presented). Thereafter, as in experiment 1, a confidence judgment task followed. Here, new judgments were followed by "Sure/Not sure" and old judgments were followed by "Remember/Know/Guess". Participants were instructed to make confidence judgments following old judgments with respect to their ability to vividly retrieve the contextually associated information related to the image during encoding. They were instructed to respond "Guess" when they were unsure about their previous Old judgment, "Know" when they recognized the scene image but could not retrieve any contextual feature linked to it, and "Remember" when the scene image brought a vivid recollection of the specific context that surrounded the encoding of that particular image during encoding.

EEG recordings and preprocessing

EEG was recorded (band-pass filter: 0.01–250 Hz, notch filter a 50Hz, and 500 Hz sampling rate) from the scalp using a BrainAmp amplifier and tin electrodes mounted in an electrocap (Electro-

Cap International) located at 29 standard positions (Fp1/2, Fz, F7/8, F3/4, FCz, FC1/2, FC5/6, Cz, C3/4, T3/4, Cp1/2, Cp5/6, Pz, P3/4, T5/6, PO1/2, Oz) and at the left and right mastoids. An electrode placed at the lateral outer canthus of the right eye served as an online reference. EEG was re-referenced offline to the linked mastoids. Vertical eye movements were monitored with an electrode at the infraorbital ridge of the right eye (EOG channel). Electrode impedances were kept below 3 kΩ. EEG was band-pass filtered offline at 0.1 - 40Hz. Independent Component Analysis (Delorme & Makeig, 2004) was applied to the continuous EEG data to remove blinks and eye movement artefacts. EEG data from two participants were lost due to technical problems and were not able to be included in the rest of the EEG analysis.

Event-related potentials (ERPs) analysis

The continuous sample EEG data were then epoched into 3100 ms segments (0 to 3000 ms relative to trial onset), and the pre-stimulus interval (-100 to 0 ms) was used as the baseline for baseline removal procedure. Trials exceeding ± 100 μV in EEG and/or EOG channels within -100 to 3000 ms time window from stimulus onset were rejected offline and not used in ERPs and time-frequency analysis (see details below). For each participant, we obtained trial epochs that were separately catalogued as belonging to Old and New conditions.

Time-frequency analysis

The power of neural oscillatory activity was calculated by means of the continuous complex Morlet wavelet (Grossmann & Morlet, 1984). It is a biologically plausible wavelet modulated by a Gaussian function which depends on the number of cycles the sinusoidal wave segment comprises. In the current study, the cycles of the Morlet wavelets used for convolution ranged from 4 to 10, increasing logarithmically as frequency increased. We adopted this modified wavelet approach to optimize the trade-off between the temporal resolution at lower frequency band and the frequency resolution at the higher frequency band. For all conditions in experiment 1 and 2, time-frequency analysis was carried out on a single trial basis, with epochs of 3500 ms time-locked to the presentation of photo starting at 500 ms before its onset. The convolution with Morlet wavelet was conducted for each frequency value from 1 Hz to 40 Hz, with 50 steps increasing logarithmically. Power values for each frequency were averaged across trials for each channel and then baseline-corrected by decibel conversion.

Cluster-based statistics of the ERP and Time-frequency data

To account for ERP differences elicited by Old and New pictures a cluster-based permutation test was used (Maris & Oostenveld, 2007) to identify clusters of significant points in the resulting spatiotemporal 2D matrix (time and electrodes) in a data-driven manner and addressing the multiple-comparison problem by employing a nonparametric statistical method based on cluster-level randomization testing to control for the family-wise error rate. Statistics were computed for each time point, and the spatiotemporal points whose statistical values were larger than a threshold ($p < 0.05$, two-tail) were selected and clustered into connected sets on the basis of x, y adjacency in the 2D matrix. The observed cluster-level statistics were calculated by taking the sum of the statistical values within a cluster. Then condition labels were permuted 1000 times to simulate the null hypothesis, and the maximum cluster statistic was chosen to construct a distribution of the cluster-level statistics under the null hypothesis. The nonparametric statistical test was obtained by calculating the proportion of randomized test statistics that exceeded the observed cluster-level statistics.

To assess for differences between Old and New conditions at the time-frequency level a similar statistical approach was adopted. However, clusters ($p < 0.05$, two-tail) were determined by connected sets of data samples that were contiguous on the basis of temporal, frequency, or spatial adjacency in the 3D matrix. Cluster statistics and null distribution were created following the same approach as for the ERP statistical approach.

Aphantasia: A case study

GB ability to retrieve individual real-life memories was examined by implementing the experimental design described in Experiment 1. More specifically, this person carried the wearable camera for 7 consecutive days and returned to the lab to perform a retrieval task while scalp EEG was acquired 1 week after encoding. The selection of the pictures depicting GB's past events (Old) and those depicting events from others (New) followed the procedure indicated in experiment 1 (total number of events = 199). EEG recording, ERP, and time-frequency analysis were similar to those described previously.

Additionally, an extensive neuropsychological screening was implemented for GB (results included in

Table 2) as well as structural Magnetic Resonance Imaging (MRI) scanning session. GB was scanned in a 3T Philips Ingenia MRI Scan (Philips Medical System) equipped with a 32-channel head coil, at the Hospital Universitari de Bellvitge of Barcelona. We used a three-dimensional fast-spoiled gradient, inversion-recovery sequence with 233 contiguous slices (repetition time, 10.43 msec; echo time, 4.8 msec; flip angle, 8°) in a 24-cm field of view, with a 320 × 320-pixel matrix and isotropic voxel sizes of 0.75 × 0.75 x 0.75 mm.

EEG and MRI data were compared to those for the group by means of the Crawford *t* statistic, which is especially suited to assessing comparisons between single subjects and group sample data (Crawford & Howell, 1998).

4.3 Results

Experiment 1

Behavioral results

Participants were highly accurate in correctly distinguishing pictures that depicted their own past (Old pictures) from those that belonged to others' past (New pictures) (**Figure 17A**). False Alarms (T1 test: Mean (M) = 0.05, Standard Deviation (SD) = 0.05; T2 test: M = 0.03, SD = 0.03; FU test: M = 0.03, SD = 0.02) and Omissions (T1 test: M = 0.08, SD = 0.06 ; T2 test: M = 0.09, SD = 0.06; FU test: M = 0.11, SD = 0.09) were very rare in all tests. However, a repeated measures ANOVA, including the three-memory test conditions (T1, T2, and FU) as a within-subject factor in the analysis, revealed that hit rate differed significantly across them ($F(2,26) = 4.94$, $p = 0.015$) (Figure 2A). A series of paired t-test comparisons showed that hit rate decreased as a function of time from encoding. Thus, significant differences were obtained when T1 and FU hit rate were compared ($t(13) = -2.68$, $p = 0.02$) but not for T1 and T2 ($t(13) = 1.37$, $p = 0.19$), nor T2 and FU ($t(13) = 1.93$, $p = 0.08$). These differences cannot be accounted for by a general decrease in performance over time as participants' ability to identify New images (i.e., correct rejections) was similar in the three tests ($F(1.29, 16.85) = 2.14$, $p = 0.16$). Correct rejections: T1 test: M = 0.94, SD = 0.05; T2 test: M = 0.97, SD = 0.03; FU test: M = 0.97, SD = 0.02).

A repeated measures ANOVA including participants' confidence ratings (Guess, Know, and Remember) on each of the three memory tests (T1, T2 and FU) revealed that participants distribution of responses concentrated around specific ratings (effect of rating: $F(2,26) = 4.94$, $p = 0.015$), and that they fluctuated differently as a function of time (effect of test: $F(2,26) = 37.99$, $p < 0.01$; interaction rating x test: $F(1.88,24.42) = 5.51$, $p = 0.01$) (**Figure 17B**). To disambiguate

this effect, we ran separate repeated measures ANOVAs including memory test as a within factor for each of the confidence ratings. We found that differences across tests were in "Know" ($F(2,26) = 4.93$, $p = 0.015$) and "Remember" ($F(2,26) = 6.31$, $p < 0.01$), but not in the distribution of "Guess" responses ($F(2,26) = 2.65$, $p = 0.09$). A series of paired t-tests revealed that "Know" responses increased over memory tests (T1 vs T2: $t(13) = -2.93$, $p = 0.01$; T2 vs FU: $t(13) = -0.74$, $p = 0.47$; T1 vs FU: $t(13) = -3.02$, $p = 0.01$) and that "Remember" responses were mostly located in memory test T1 (T1 vs T2: $t(13) = 2.03$, $p = 0.06$; T2 vs FU: $t(13) = 1.74$, $p = 0.11$; T1 vs FU: $t(13) = 3.43$, $p < 0.01$).

We next examined participants' proportion of emotional rating to the correctly retrieved pictures over tests (T1, T2 and FU). This showed that participants rarely indicated maximum negative (i.e., -2 in the scale) or positive (i.e., +2) emotion in the tests (negative: M = 1.14%, SD = 1.94%; positive: M = 14.35%, SD = 13.61%; respectively across the three tests). Therefore, we grouped -2 and -1 responses as negative and +1 and +2 as positive, leaving 0 as indicating neutral emotion. A repeated measures ANOVA, including time (T1, T2, and FU) and emotion (negative, neutral, and positive) as within subject factors, revealed a main effect of emotion ($F(1.13,14.65) = 22.52$, $p < 0.01$) but a non-significant emotion x time interaction ($F(1.62,21.11) = 0.72$, $p > 0.05$) (**Figure 17C**). To identify the source of this main effect, we averaged the proportion of each emotion's category across the three tests. A series of paired t-test comparisons revealed that most pictures elicited neutral emotion in the participants (neutral vs negative: $t(13) = 8.02$, $p < 0.01$; neutral vs positive; $t(13) = 0.01$, $p = 0.99$) and positive emotion (positive vs negative: $t(13) = 7.53$, $p < 0.01$).

Finally, participants' response accuracy to temporal order memory was at random (M = 0.49, SD = 0.22), thereby indicating this test was not suitable to capture the participants' ability to retrieve temporal representations of their own AMs.

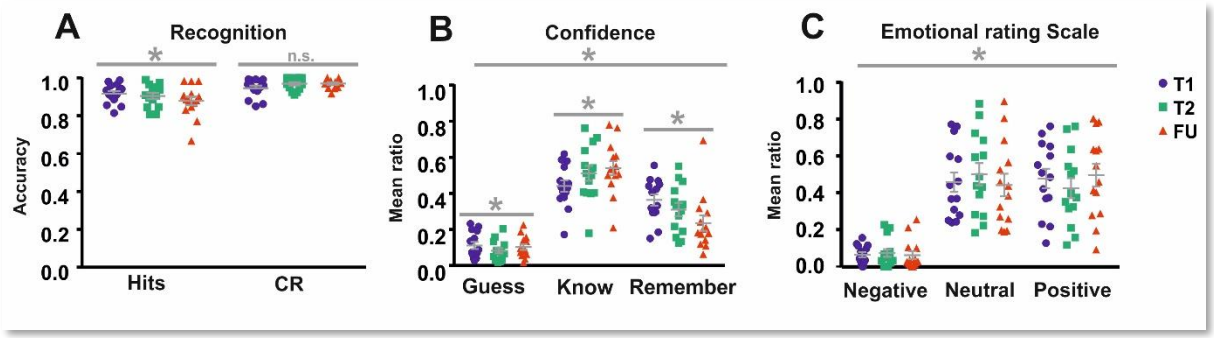


Figure 17. Behavioral data in healthy young participants from Experiment 1. **(A)** Averaged participants' accuracy and correct rejections in selecting their own events (old) compared to others' events (new) over three time periods (T1: one week, T2: two weeks, FU: 6 to 12 months). **(B)** Confidence judgments over three time periods (T1, T2, and FU). **(C)** Emotional ratings over three time periods (T1, T2, and FU). The asterisks indicate significant ($p < 0.05$) effects. Error bars represent SEM.

ERPs results

Our analytical strategy was to first assess whether Old and New images elicited different patterns of brain activity in the participants. To address this issue, we averaged, at the participant level, the ERPs elicited by Old and New image conditions across tests and ran a cluster-based permutation test between these two conditions. This analysis revealed a significant cluster showing that Old images elicited higher ERP positive amplitude from 400 ms at stimulus onset, which lasted over the rest of the temporal window in the analysis and comprised a large distributed area over the scalp (**Figure 18A**). To assess how the identified Old/New ERP effect varied as a function of memory test, we submitted the averaged ERP activity from the cluster to a repeated-measures ANOVA including experimental condition (Old, New) and memory test (T1, T2, and FU) as a within-subject factor. As expected, this analysis revealed a main effect of condition ($F(1,11) = 60.24$, $p < 0.01$) and a significant condition x memory test interaction ($F(2,22) = 6.45$, $p < 0.01$) (**Figure 18B**) but not a main effect of memory test ($F(2,22) = 0.79$, $p = 0.47$). However, separate repeated-measures ANOVAs for ERP values to Old and New images revealed that none of them showed a statistically significant effect as a function of memory test (Old: $F(2,22) = 0.66$, $p = 0.53$; New: $F(2,22) = 2.58$, $p = 0.1$).

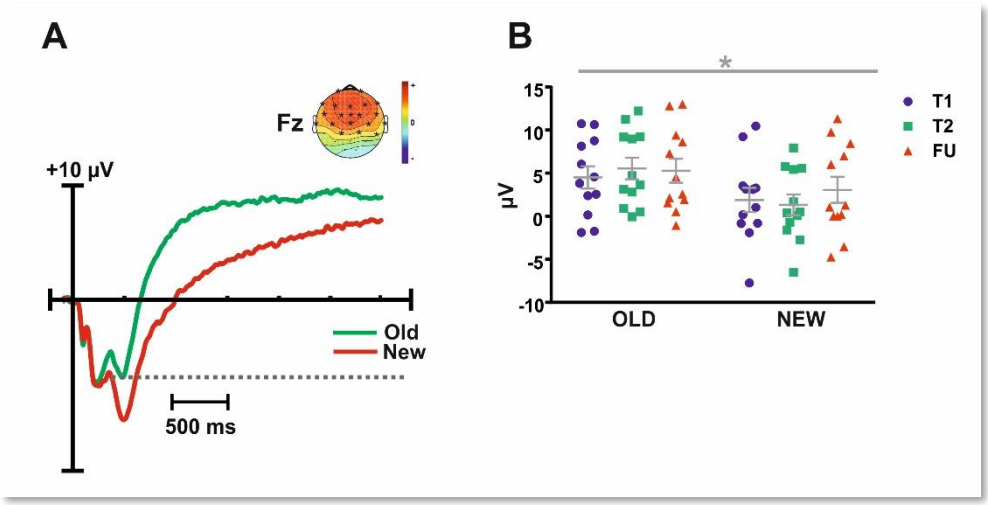


Figure 18. **(A)** Across participants grand-average Event-Related Potentials (ERPs) for Experiment 1 for Old and New conditions at Fz. A cluster-based permutation analysis between the two conditions revealed that Old pictures elicited greater ERPs amplitude over fronto-central scalp regions. Dashed line indicates the temporal window of significance ($p < 0.05$, corrected) **(B)** Cluster-averaged Individual ERP data for each of the three recognition memory tests and conditions (T1, T2, and FU). * indicates $p < 0.05$. Error bars represent SEM.

Time-frequency results

Following the ERP analytical strategy, we first implemented a cluster-based permutation test to identify, in a data-driven manner, for the existence of a main Old/New difference pattern of neural oscillatory response along the temporal x spatial x spectral dimension. Thus, spectral power measures elicited at the onset of Old and New correct responses were averaged across the three tests (T1, T2, and FU) and were then compared. This analysis revealed the existence of a significant cluster initiating at around 1000 ms from stimulus onset comprising mostly low-frequency activity in the theta range (4-8Hz) (**Figure 19A**). More specifically, these results showed that Old responses were accompanied by a decrease in theta power and that this effect was over frontal and central regions of the scalp. A repeated-measures ANOVA, including as within-subject factors memory test (T1, T2 and FU) and image type (Old and New), showed a main effect of image type ($F(1,11) = 56.85$, $p < 0.01$), no significant main effect of memory test ($F(2,22) = 0.33$, $p = 0.73$), but the existence of a significant image type x memory test interaction ($F(2,22) = 5.15$, $p = 0.01$) (**Figure 19B**). These results suggest that theta Old/New effect differed between memory tests. However, paired t-test analysis showed that Old vs New theta differences were significant at T1 ($t(11) = 4.21$, $p < 0.01$), at T2 ($t(11) = 7.21$, $p < 0.01$), and at FU ($t(11) = 3.69$, $p < 0.01$), thereby hindering the possibility of establishing the source of this interaction clearly in our data.

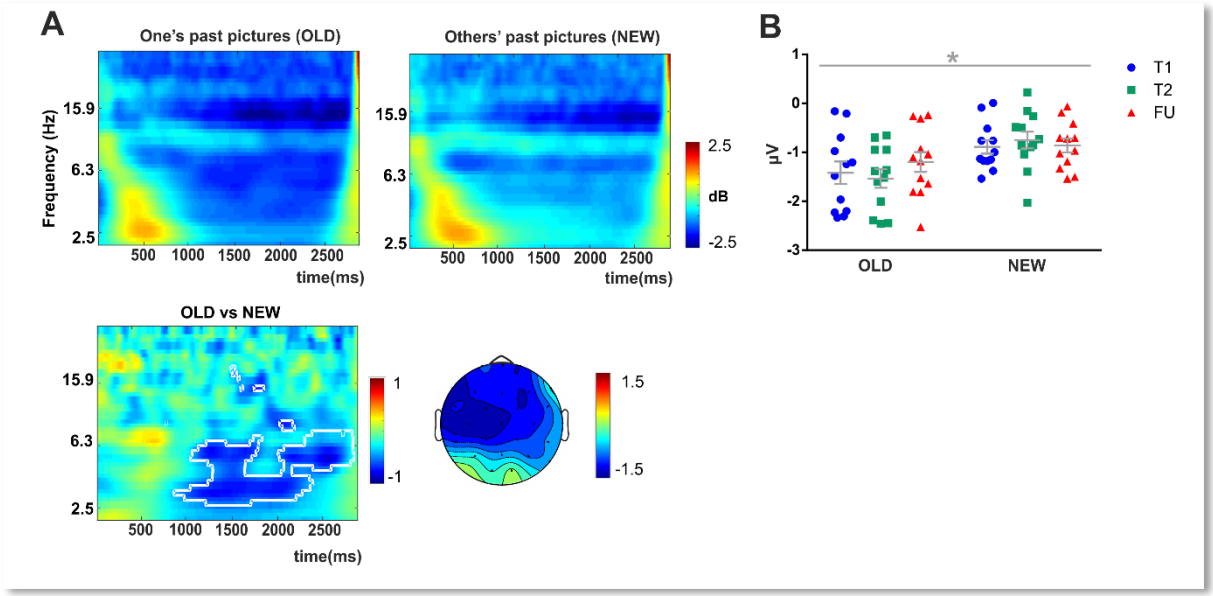


Figure 19. Theta oscillations in Experiment 1. **(A)** Group-averaged changes in spectral power over the three periods of time (averaged over all scalp sensors) elicited by pictures related to own personal events (old) compared to other's events (new). Decreased theta power was observed in old responses over fronto-central regions of the scalp. **(B)** Average theta power over three periods of time (T1, T2, and FU). Significant ($p < 0.05$) interaction effect is indicated with a grey star. Error bars represent SEM.

Experiment 2

Behavioral results

Participants' Hits and Correct Rejections (CR) rates are displayed in **Figure 20A**. Overall, Participants' performance was much poorer in this experiment. To assess this statistically, we compared participants' Hits and CRs in experiment 1 and in experiment 2. This analysis used participants' behavioral data obtained in condition T1 from experiment 1 as this was the one that shared a one-week time frame between encoding and retrieval in the two experiments. This analysis confirmed significant differences in the proportion of Hits ($F(1,13) = 47.09$ $p < 0.01$) and in CRs ($F(1,13) = 31.12$, $p < 0.01$) between experiments, thereby indicating, as expected, participants were much accurate in recognizing pictures related to their own past real-life experience than those encoded "artificially" in a lab-context.

In addition, a repeated-measures ANOVA on participants' confidence ratings revealed they ratings following correct Old responses were unequally distributed ($F(2,26) = 20.720$, $p < 0.01$; **Figure 20B**). More specifically, participants tended to rate as having "guessed" more frequently than "remembered" the correctly recognized scene images, thereby indicating that memory accuracy was, overall, quite low. When comparing confidence ratings provided in the analogous experiment 1, we found a significant interaction effect of confidence ($F(2,26) = 42.26$, $p < 0.01$), thereby indicating confidence rating distribution differed between experiments. These results indicated that participants' sense of recollection for laboratory-based was not as vivid as when they judged their own stimuli.

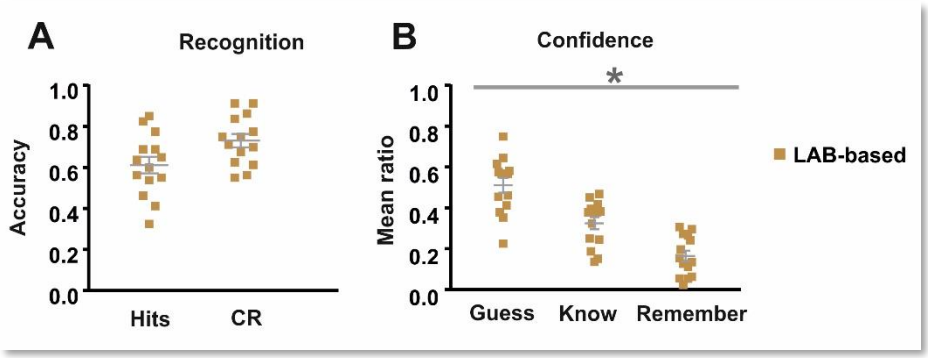


Figure 20. Behavioral data in healthy young participants from Experiment 2. **(A)** Averaged participants' accuracy and correct rejections in selecting pictures previously encoded (old) compared to pictures never seen (new). **(B)** Confidence judgments based on laboratory stimuli. The asterisks indicate significant ($p < 0.05$) effects. Error bars represent SEM.

ERPs results

EEG data was analyzed as in experiment 1, by contrasting ERP patterns of activity elicited by Old and by New images through a data-driven cluster-based permutation test. This analysis revealed a significant cluster revealing that Old images elicited higher ERP positive amplitude from 400 ms at stimulus onset. However, compared to ERP differences observed in experiment 1, this cluster of EEG activity was much shorter and less distributed over the scalp (**Figure 21A**). Nevertheless, a repeated-measures ANOVA including response type (Old and New) and experiment (T1 from experiment 1 and experiment 2) as within-subject factor, revealed Old/New ERP effects were statistically similar in the two experiments (main effect of experiment: $F(1,9) = 1.96$, $p = 0.19$; experiment x response type interaction: $F(1,9) = 3.29$, $p = 0.10$).

Time-frequency results

The implementation of a cluster-based permutation test assessing for differences between Old and New responses to scene images encoded in the laboratory yield non-significant along the temporal x frequency x spatial (scalp sensors) dimensions (**Figure 21B**). Thus, contrary to the theta Old/New effects found in experiment 1, differences were not observable in experiment 2. Nevertheless, to assess the extent to which the Old/New theta effects found in experiment 1 differed from the same theta modulations in experiment 2, we ran a repeated-measures ANOVA including response type (Old and New) and experiment (T1 from experiment 1 and experiment 2) as within-subjects factors. Given the null effects found in experiment 2, theta power in this experiment was extracted by averaging data points that were within the temporal x frequency x spatial cluster data points identified in experiment 1. This analysis confirmed the main effect of image type ($F(1,9) = 9.57$, $p = 0.013$) but uncovered no significant main effect of the memory test ($F(1,9) = 1.96$, $p = 0.195$) nor type x memory test interaction ($F(1,9) = 3.29$, $p = 0.103$), which hindered the possibility of concluding that the Old/New ERP effect was greater in one of the experiments. However, note that the clusters of activity included in this analysis were much larger in ERPs from experiment 1 than in ERPs from experiment 2.

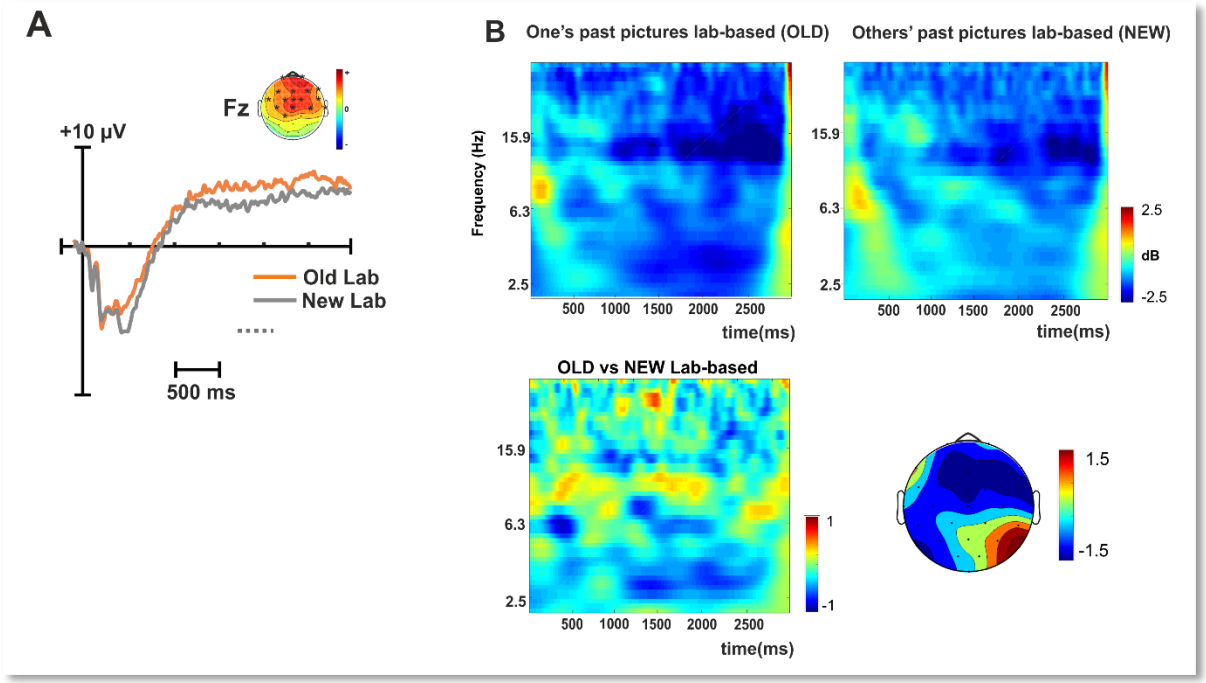


Figure 21. (A) Across participants grand-average Event-Related Potentials (ERPs) for Experiment 2 for Old and New conditions at Fz. A cluster-based permutation analysis between the two conditions revealed that Old pictures elicited greater ERPs amplitude over fronto-central scalp regions. Dashed line indicates the temporal window of significance ($p < 0.05$, corrected) **(B)** Group-averaged changes in spectral power (averaged over all scalp sensors) elicited by pictures related to own personal events (old) compared to other's events (new). Decreased theta power was observed in old responses over fronto-central regions of the scalp.

Case GB (Aphantasia)

Behavioral data

GB was highly accurate in identifying images that belonged to his past (Hit rate = 0.91) and those that did not (Correct Rejection rate = 0.05). However, hits were mainly "Known" judgments (rate of 0.57; Guess rate = 0.03 and Remember rate = 0.29), thereby indicating that his ability to correctly recognize Old pictures was usually not accompanied by a detailed or vivid recollection of the cued AM event episode.

In order to evaluate statistically the extent to which case GB's behavioral performance was similar to the sample of participants from experiment 1, we compared each of the behavioral measures between the single case and group sample at T1 by means of the Crawford t-test. However, none of the comparisons proved to be statistically significant (all $p > 0.05$).

EEG (ERPs and Time-Frequency data)

A clear Old/New ERP effect was found in case GB (**Figure 22A**). ERPs to Old and New responses were similar to those found in the sample group that participated in experiment 1. Thus, differences between ERPs were displayed at frontal and central scalp regions and they began at around 400 ms from stimulus onset and persisted over the 3000 ms epoch window. This was confirmed by the finding that the ERP to Old and New stimuli in GB and in the participants from experiment 1 was statistically similar (all, $p > 0.05$).

The time-frequency analysis, however, showed no clear differences between Old and New responses in case GB (**Figure 22B**). Although this lack of visible theta effect for GB was in contrast to the theta decrease to Old response in participants from experiment 1, Crawford t-test analysis between the two sets of data showed that they were not statistically different (all, $p > 0.05$).

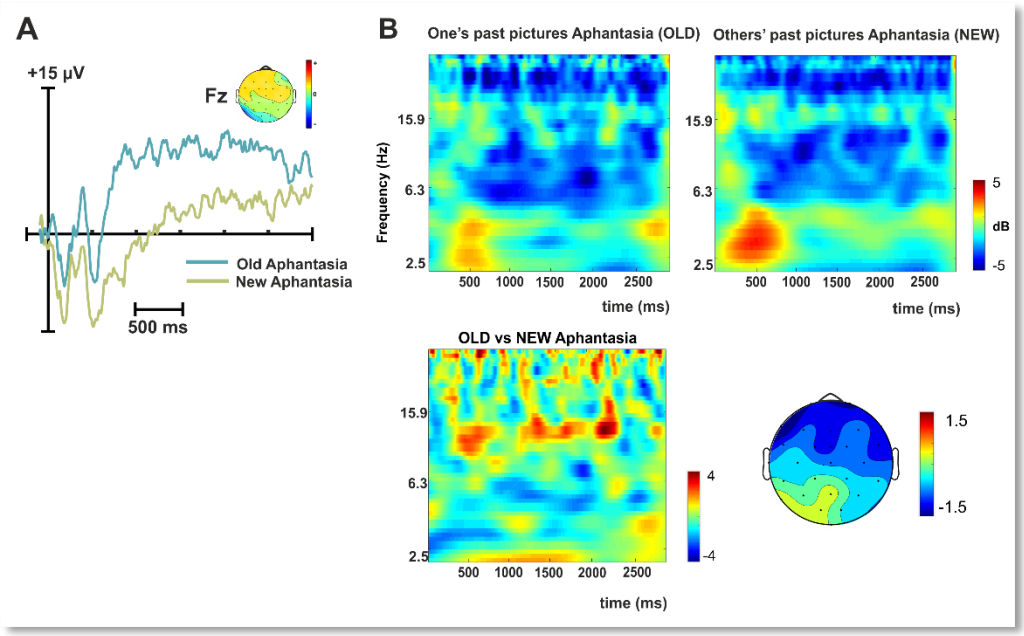


Figure 22. (A) Event-Related Potentials (ERPs) for Experiment 3 (case GB) for Old and New conditions at Fz. Old pictures elicited greater ERPs amplitude over fronto-central scalp regions. **(B)** Changes in spectral power (averaged over all scalp sensors) elicited by pictures related to own personal events (old) compared to other's events (new). Decreased theta power was observed in old responses over fronto-central regions of the scalp.

4.4 Discussion

Real-life experience is characterized by continuous inputs carved by memory systems into an organized, yet intricate, memory network of episodic event representations. How our memory systems are capable of retrieving our unique past episodic experience is a current hallmark in the

Autobiographical Memory (AM) research field. In the current study, we proposed a novel methodological approach that combined the use of a wearable camera and implementation of a deep neural network-based algorithm to assess how individuals retrieve specific event episodes from their own past daily life routines. This approach was successful in automatically identifying pictures sequence that represented unique episodic events, thereby reducing the number of "items" and allowing us to explore memory retrieval for the entire past experience relatively rapidly in a later memory test. Our findings revealed that participants were highly accurate in recognizing pictures depicting their own past but that the quality of the retrieved memories changed with the passing of time. Specifically, we found that participants tended to "Remember" with greater accuracy the memory episodes cued by pictures one week after their encoding (test T1), and that this shifted towards a higher proportion of "Know" responses two weeks after (test T2) and 6 to 14 months after (test FU) encoding, thereby suggesting that forgetting was a consequence of the passing time. In line with this behavioral pattern, we found that two well-known electrophysiological brain markers of successful episodic memory retrieval, the Old/New ERP effect and theta neural oscillations, appear clearly associated with the participants' ability to correctly recognize pictures that cued self-experienced past events from real life, and less clearly, but also evidently, to neutral pictures depicting indoor and outdoor scenes encoded in the lab. Finally, in an attempt to validate this experimental approach at the single-subject level, we presented the data from a single case with Aphantasia, who showed a lack of visual imagery despite having all other cognitive abilities intact.

In experiment 1, we examined the ability of healthy adults to retrieve autobiographical memories of real-life event episodes encoded over a period of a week. We found that participants were highly accurate in doing so but that the quality of the retrieved memories decreased over time, as they reported that picture cues were less prone to eliciting a vivid recollection of the episodic context associated with the picture. This increase in the feeling of familiarity might be explained by the expected decline in memory strength over time that could cause the loss of contextual features, attributed to an inherent time-dependent memory transformation due to consolidation processes. Indeed, during consolidation, memories could lose specific details, becoming more schematic and context-independent with a resulting 'semantization' (Winocur & Moscovitch, 2011). These changes could be structurally related to a reorganization of the representational patterns within the hippocampus (Dandolo & Schwabe, 2018), shifting the participants' judgments from relying on more detailed information when memories are recent, to more gist-based judgments when these memories are remote.

A widely accepted idea is that the retrieval of AMs engages multiple cognitive processes, including the controlled searching process triggered by the cue to a combination of sensory, emotional, and perceptual elements that are needed to come together and emerge as a specific episodic memory (Conway, 2009). This complex process is thought to engage the coordination of several neural networks including the medial prefrontal cortex (PFC), posterior parietal cortex, and medial temporal lobe (MTL) regions, including the hippocampus (Svoboda & Levine, 2009). Previous studies have also attempted to establish a specific role for each of these brain regions. For example, the involvement of the PFC has been attributed to the need to engage a self-reference process and the parietal regions to strategic search and attentional demands (St. Jacques et al., 2011). Our study was blind to the neural sources that were involved at retrieval but, we did find that successful retrieval of AMs was accompanied by modulations of large-scale neural oscillatory patterns in the theta range (4-8Hz). It has been suggested that, through theta oscillations, the MTL may drive the reciprocal exchange of information with neocortical areas (Sirota et al., 2008). Accordingly, the MTL may actively control the transfer of neocortical information to the MTL itself via theta-phase biasing of neocortical network dynamics (Sirota et al., 2008), as postulated in several computational models of memory (Marr, 1971; McClelland et al. 1995; Rolls, 2000; Treves & Rolls, 1994), and this may also account for recent evidence from human intracortical recordings (Foster et al., 2013) and, noninvasively, via magnetoencephalography (Fuentemilla et al., 2014) of MTL-neocortical theta phase-locking during the retrieval of AMs. An interesting issue that remains elusive is why some studies find theta power increases with successful retrieval while others find the opposite pattern, with theta power decreasing, as in the current study. This issue is a topic of intense debate in the research community (see for example Herweg et al., 2019). Nevertheless, our finding, that theta power engagement tends to decrease as a function of memory age (e.g., T1 vs FU), lends support to the notion that MTL-neocortical theta activity decreases over time. This would address the possibility that the MTL regions become less necessary for the retrieval of remote AMs as opposed to recent AMs and therefore support the prediction from system consolidation theory that posits that memories become hippocampus-independent upon their consolidation over time (Diekelmann & Born, 2010).

Interestingly, naturalistic stimuli have received increasing interest in the design of experimental paradigms with videos, short films, and the expansion of virtual reality. Retrieving naturalistic stimuli, such as autobiographical event episodes, requires exploration through a wide search space, the integration of information across multiple time scales, and the activation of self-referential processes and vividness that typically accompany the successful retrieval of ones' past (Cabeza et al., 2004; Chen & Caplan, 2017; Chow & Rissman, 2017; Gilboa et al., 2004; McDermott et al., 2009; Roediger & McDermott, 2013). Our findings indicate that cueing AMs through pictures

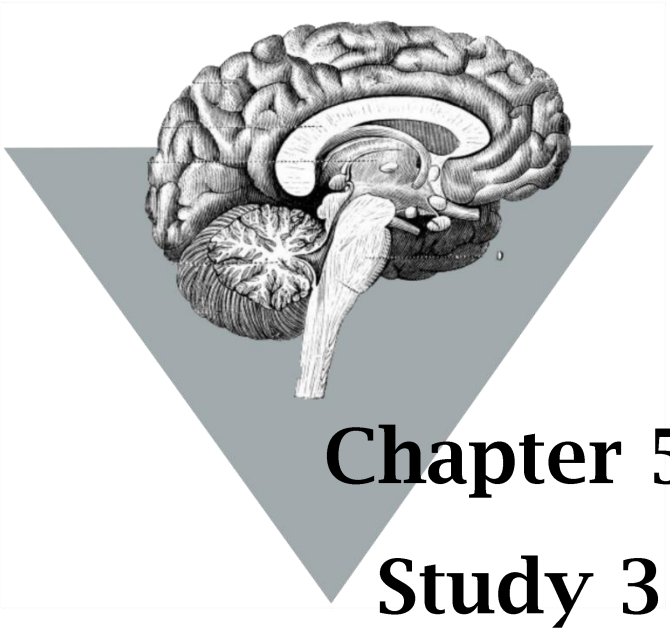
recorded from a wearable camera was effective in eliciting this amalgam of cognitive and neural processes, as the magnitude of the behavioral and EEG effects was large and consistent, whereas these effects were minimal or less clear when the same individuals retrieved picture scenes encoded at the lab. Thus, the possibility of studying the retrieval of AMs from real-life experience and at the individual level represents a promising avenue that may have implications at the clinical level, as this can be applied patient by patient, to study memory functioning in daily life routine. Another advantage of our approach is that it may be useful in exploring AM functioning in participants with unusual characteristics that are difficult to treat at the group level in the general population, such as the subject included here with Aphantasia.

Overall, we provide evidence of a novel methodological approach to exploring AMs that is effective in assessing the ability of an individual to retrieve memories from a single event episode that took place in real-life. Our findings help contribute to the emerging body of literature emphasizing the advantages of using naturalistic material rather than artificial lab-based stimuli to explore the cognitive and neural underpinnings of episodic memory. Current findings may be relevant beyond basic research as they may help improve understanding of AM functioning in the clinic at the individual level.

Table 2. Neuropsychological tests and results from case GB (Experiment 3).

COGNITIVE DOMAIN	COGNITIVE PROCESS	TEST	RAW SCORE	NORMATIVE SCORE
PERCEPTION	Visual Perception	Poppelreuter Overlapping Figures	40/40	100%
	Spatial Organization	Rey Osterrieth Complex Figure-Copy	32	SS=9
	Face Recognition	Famous faces recognition test-Spanish Adaptation	69/75	92%
MEMORY	Immediate Visual Memory	Rey Osterrieth Complex Figure - Immediate recall	27 (type III)	SS=13
		Wechsler Memory Scale (WMS) III - drawings	102	SS =17
	Delayed Visual Memory	Rey Osterrieth Complex Figure - delayed recall	27 (type III)	SS = 13
		Wechsler Memory Scale (WMS) III - drawings	72	SS = 10
	Visual Recognition	Wechsler Memory Scale (WMS) III - drawings	47	SS = 12
	Immediate Verbal Memory	Wechsler Memory Scale (WMS) III - Short Stories I	22	SS = 6
	Verbal Learning Index	Wechsler Memory Scale (WMS) III - Short Stories I, B2 (learning)	5	SS = 11
		Rey Auditory Verbal Learning Task part A1-A5	55	Z= 0.17
	Delayed Verbal Memory	Wechsler Memory Scale (WMS) III - Short Stories II	26	SS = 10
		Rey Auditory Verbal Learning Task (RAVLT)	2	Z = -3.4
	Verbal Learning Curve	Rey Auditory Verbal Learning Task (RAVLT) A1-A2-A3-A4-A5	7-11-10-12-15	(Z) 0.16; 0.5; -0.64; -0.1; 1.21

	Resistance to interference	Rey Auditory Verbal Learning Task (RAVLT)	12	Z= 2.75
	Verbal Recognition	Wechsler Memory Scale (WMS) III - Short Stories II	27	SS = 11
		Rey Auditory Verbal Learning Task - Recognition	15	Z = 0.67
	Auditory memory (music)	Montreal Battery of Evaluation of Amusia (MBAE)- task 1 (scale)	26/31	Z= -0.43
EXECUTIVE FUNCTION		Wechsler Adult Intelligence Scale (WAIS) III - Digit Span (forward and backward)	20	SS = 13
		Wechsler Adult Intelligence Scale (WAIS) III – Letters and numbers	14	SS = 15
		Rey Osterrieth Complex Figure - Copy	Type III	-
		Wechsler Adult Intelligence Scale (WAIS) III - Cubes	62	SS = 18
		Wisconsin Card Sorting Task (WSCT)	9 errors	T = 50
		Tower of London (TOL) total correct responses	10	SS =18
		Tower of London (TOL) total number of excessive numbers	19	SS = 11
		Semantic (animals)	26	SS = 11
		Phonological (letter *p*)	16	SS = 10
INTELLIGENCE ESTIMATES		Wechsler Adult Intelligence Scale (WAIS) III - Vocabulary	53	SS = 14
		Wechsler Adult Intelligence Scale (WAIS) III - Similarities	22	SS = 12
		Raven Matrices (General Scale)	54/60	Normative score
SELF-RATED MEASURES		Vividness of Visual Imagery Questionnaire Revised (VVIQR)- Spanish version	8/224	Z= -5.72



Chapter 5

Study 3

This study corresponds to:

Nicolás B, Sala-Padro J, Naval P, Rossello A, Falip M, Camins A, Fernandez-Coello A, Rico I, Cucurell D, Cámara E, Fuentemilla L. (2020). Brain regions supporting the retrieval of real-life autobiographical memories collected with a wearable camera at individual level: a preliminary fMRI study.

Chapter 5: Study 3

Brain regions supporting the retrieval of real–life autobiographical memories collected with a wearable camera at individual level: a preliminary fMRI study

Most of the behavioural and neuroimaging studies of episodic retrieval have used laboratory stimuli as memory cues. However, the encoding of events in naturalistic scenarios has revealed that autobiographical stimuli have more personal relevance and are more complex, including information about the visuospatial, temporal, social and emotional contexts. Functional neuroimaging has revealed that the retrieval of autobiographical memories involves the interaction of multiple networks and systems such as the medial PFC network, the Medial Temporal Lobe network, and the frontoparietal network. In this study we aimed to test the extent to which picture cues, collected by healthy adults through a wearable camera, elicited the activation in these neural networks during memory retrieval of real-life autobiographical memories. Our findings revealed participants were highly accurate during retrieval and that this was accompanied by the engagement of known retrieval-related brain networks. The current study will help to validate the effectiveness of current retrieval design protocol to examine real-life autobiographical memories at individual level.

Justification of the inclusion of this preliminary study in the thesis:

Though this is still an ongoing study, I reasoned it deserved a special place in the thesis for the following reasons. First, one of the objectives of the current thesis work was to provide strategies to evaluate memory functioning in real-life and, if possible, to bring an opportunity to be implemented in the clinics. Second, many of the theoretical questions and mechanistic questions raised in the thesis place a central role in MTL structures, difficult to assess via scalp EEG. Third, the fact that the study is at the preliminary stages is a natural consequence of a project that takes time to be implemented in clinical settings and may inevitably take longer than a PhD program. All in all, despite the evidence provided in this study remains at preliminary stage, I believe it is still highly informative and valuable to the current thesis and therefore I decided to include it as a third and last study project.

5.1 Introduction

Autobiographical memory (AM) retrieval encompasses multiple processes that combine personal knowledge with current goals, strategic search, constructive processes and the recovery of a memory trace with varying degrees of re-experience. Therefore, recalling memories from our personal past includes a distributed set of regions along separated memory systems (Cabeza & St Jacques, 2007; Svoboda et al., 2006), such as those supporting self-reference, search, memory consolidation and storage and goal-related processes (Rubin, 2006; St. Jacques et al., 2011).

Functional neuroimaging studies have identified a number of regions as medial and lateral prefrontal cortices (PFC), lateral and medial temporal lobes (MTL; Hippocampus and parahippocampal gyrus), ventral parietal cortex and posterior cingulate cortex (Cabeza & St Jacques, 2007; McDermott et al., 2009; Svoboda et al., 2006) that are frequently involved during autobiographical memory (AM) retrieval. One of the primary networks recruited overlaps with the default mode network that is composed of two subnetworks: A medial prefrontal cortex network (PFC) that includes dorsal medial PFC, posterior cingulate and ventral parietal cortices (Andrews-Hanna et al., 2010; Buckner, Andrews-Hanna, & Schacter, 2008), and an MTL network that comprises hippocampal, ventral medial PFC, retrosplenial and ventral parietal cortices (Kahn et al., 2008; St. Jacques & De Brigard, 2015; Vincent et al., 2006). The medial PFC network is associated with self-referential processes (St. Jacques et al., 2011), while the MTL network has been related to the scene-construction and to recollection processes during AM retrieval (e.g. hippocampus; Diana, Yonelinas, & Ranganath, 2007). Another important neural network involved in AM retrieval is the frontoparietal or central executive network. This network includes the lateral PFC, anterior cingulate and inferior parietal cortices that are engaged during control operations that act on memory (Cabeza et al., 2008; Moscovitch & Winocur, 2002). The lateral PFC activity is predominantly left-lateralized (Svoboda et al., 2006) reflecting the contribution of complex retrieval processes and semantic memory (Conway, Pleydell-Pearce, & Whitecross, 2001; Svoboda et al., 2006).

In this preliminary study, we sought to examine whether these set of neural networks are engaged during the retrieval of AMs for single event episodes cued by pictures recorded by each participant through a wearable camera for 4 full consecutive days. To address this issue, we asked 5 healthy adults to enroll in the experiment and tested their retrieval accuracy for event episodes encoded one week ago while BOLD signal from functional Magnetic Resonance Imaging (fMRI) was acquired.

5.2 Materials and methods

Participants

The participants included in this study are part of a control group that matched individuals with TLE (see Future research directions) in an ongoing autobiographical memory study that we are currently developing at Hospital de Bellvitge (Barcelona). In this study, we have included five of them (2 females, right-handed, average age at scan: 36.8 years old (SD = 13.93), average education years: 12.4 (SD = 2.30)) who gave written informed consent in accordance with a research protocol approved by the Hospital of Bellvitge Ethics Board (Barcelona). All participants were fluent in Spanish and had no history of significant psychiatric or neurologic disorder.

Materials

We used the wearable camera Narrative clip 2 camera® (http://getnarrative.com/) with a camera sensor of 8MP and a resolution of 3264x2448(4:3). The camera was programmed to automatically take images every thirty seconds and produced pictures with an egocentric perspective. Participants were instructed to wear the device on a lanyard around the neck. The characteristics of the pictures and information about the design are presented in Study 2 (see Chapter 4). Narrative clip 2 incorporated a downloading app that allowed participants to download the pictures directly to a hard drive. Participants were instructed to not watch the pictures until the experiment finalized. None of the participants reported to have done so at the end of the study.

Design overview

Participants were asked to come to a training session two weeks before the scanning session. They were informed about how the wearable camera worked and they read, understood and signed the informed consent. We provided details on privacy issues so that all participants were fully aware of them before the study began. In the current study, participants wore the wearable camera for a period of 4 days. The data collection period was established from morning to evening (which included ~12h of recording time). Once participants finished data collection, they were requested to return the materials to be processed and were tested one week after. Participants confirmed not having checked the pictures during the recording days. Participants returned to the lab to be tested one week after data collection.

For practical reasons (i.e., lack of computing power), in this study, single event episodes were identified from the sequence of collected pictures manually instead of using the SR-Clustering

algorithm used in study 2 (see Chapter 4). However, similar criteria based on contextual and semantic congruency was used, subjectively, to chunk each participants' sequences of collected pictures into separate event episodes. Each participant's event was then inspected and those which displayed non-meaningful episodes (e.g., all pictures were blurred, or when the camera was pointing to the roof or they were blocked by clothes) were discarded from the study. Picture events that described interactions with participants' relatives were excluded from the study. As in our previous study, a representative picture for each of the resulting events was selected and used to cue a specific memory during the subsequent memory test. Pictures cues presented to one participant depicting her own past (Old) were also presented to another participant as New images. This ensured that differences between Old and New pictures presented to each participant were only based on a direct link to ones' past while preserving the rest of the characteristics intact during the test (e.g., angle of view, picture image features, description of routine daily life activities).

Autobiographical memory retrieval task

Participants performed a simplified version of the recognition memory test used in our previous EEG study (Study 2; Chapter 4) (see **Figure 23**). In the current version of the test, pictures were presented on the screen for 3000 ms preceded by a 1000 ms fixation cross. Each picture was followed by an 'OLD/NEW' message on the screen, upon which participants were required to judge whether the picture cued an event from their own daily life (OLD) or whether it was experimentally novel (NEW). A confidence judgment by a 'Sure/Not sure' forced-choice option response followed. The participants were instructed to make confidence judgments following Old judgments with respect to their ability to recollect events depicted in the pictures with the context in which they occurred.

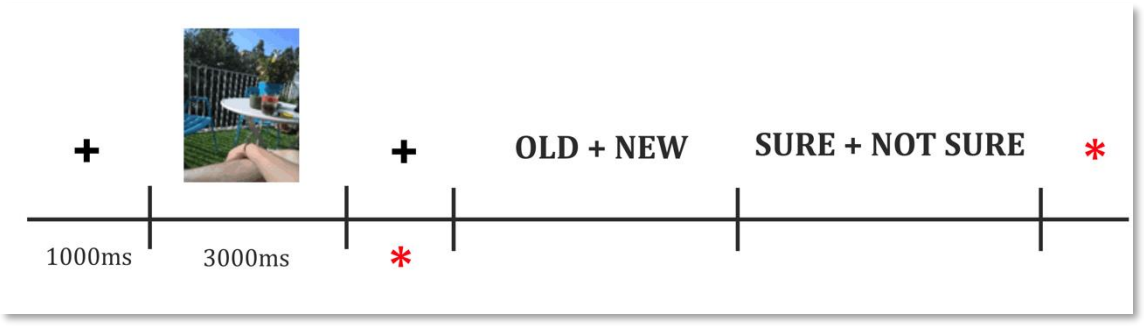


Figure 23. Autobiographical memory task. Indicated by a red star: Variable Jittering between 1000 – 2000 ms intervals of 250 ms (1000, 1250, 1500, 1750, and 2000).

fMRI data acquisition and processing

Participants were scanned in a 3T MRI Scan Philips Ingenia, Philips Medical System, 32-channel head coil, at the Hospital Universitari de Bellvitge of Barcelona. Structural images comprised a conventional high-resolution T1-weighted image, 181 sagittal slices, repetition time (TR) = 7.8 ms, echo time (TE) = 3.6 ms, flip angle = 8 degrees, size of acquisition matrix 232 x 191, FOV= 2.3 cm, 1 mm isotropic voxel with no gap between slices. Functional images were acquired in the axial plane using a single-shot T2-weighted gradient-echo EPI sequence with a TR= 3000 ms, TE= 25 ms, flip angle = 90 degrees, Voxel size = 3 × 3 × 3 mm^3, FOV = 24 cm, size of acquisition matrix 80 × 79 ×50.

Data analysis

fMRI data analysis

Pre-processing and statistical analysis of fMRI data were performed using SPM12 software package (Welcome Department of Imaging Neuroscience Group, London, UK) running on MATLAB (v17a, Mathworks, Natick, MA). The preprocessing steps included slice timing adjustment correction to minimize acquisition timing differences between slices and realignment for head motion correction. Co-registration between the functional and the structural T1-weighted image, segmentation of the T1-weighted image into different tissues, DARTEL normalization of the functional and structural images to the MNI space using the parameters derived from the segmentation of the T1-weighted image. Finally, images were spatially smoothed with an 8 mm isotropic Gaussian kernel.

Statistical analysis was carried out using a General Linear Model based on a least-square estimation (GLM; Friston, Frith, Turner, & Frackowiak, 1995) in which OLD and NEW conditions were modeled with a regressor waveform convolved with a canonical hemodynamic response function. Data were high pass filtered (to a maximum of 1/128 Hz) and serial autocorrelations were estimated using an autoregressive model. Resulting estimates were used for non-sphericity correction during the model estimation. Confounding effects in global mean were removed by proportional scaling and signal correlated motion effects were minimized by including the estimated movement parameters in the model. After model estimation, the main effect of each condition was calculated, and the main contrast of the analysis was implemented: OLD vs. NEW.

Finally, first-level contrast images were entered into a second-level analysis using a one-sample t-test including all controls together.

Effects were reported at a whole-brain level if they exceeded a voxel-wise threshold of $p < 0.001$ ($k > 80$ voxels extent). For the figures, a threshold of $p < 0.001$ uncorrected at the whole-brain level was used. Anatomical areas were identified using the Automated Anatomical Labeling Atlas (Tzourio-Mazoyer et al., 2002) included in the xjView toolbox (http://www.alivelearn.net/xjview8/).

5.3 Results

Behavioural results

Participants were highly accurate in recognizing pictures depicting their own past experience (Old pictures) from those depicting novel scenarios (New pictures). Overall, they were correct on 0.95 (± 0.03) of the Old trials, were incorrect on 0.05 (± 0.03) and were unsure on 0.08 (± 0.085). When excluding unsure responses from analysis, the mean hit rate was 0.87 (± 0.11), and the mean false alarm rate was 0.03 (± 0.04), indicating that participants rarely recognized pictures from other participants as their own.

fMRI results

One sample t-test comparison between Old and New conditions revealed significant ($p < 0.001$, FEW cluster level corrected) greater BOLD signal in the right hippocampus, the middle temporal gyrus, the posterior middle temporal gyrus, and the posterior temporal supramarginal gyrus, the left posterior cingulate gyri and the anterior cingulate bilaterally, and the orbitofrontal areas, with a left-sided predominance. (**Figure 24** and **Table 3**)

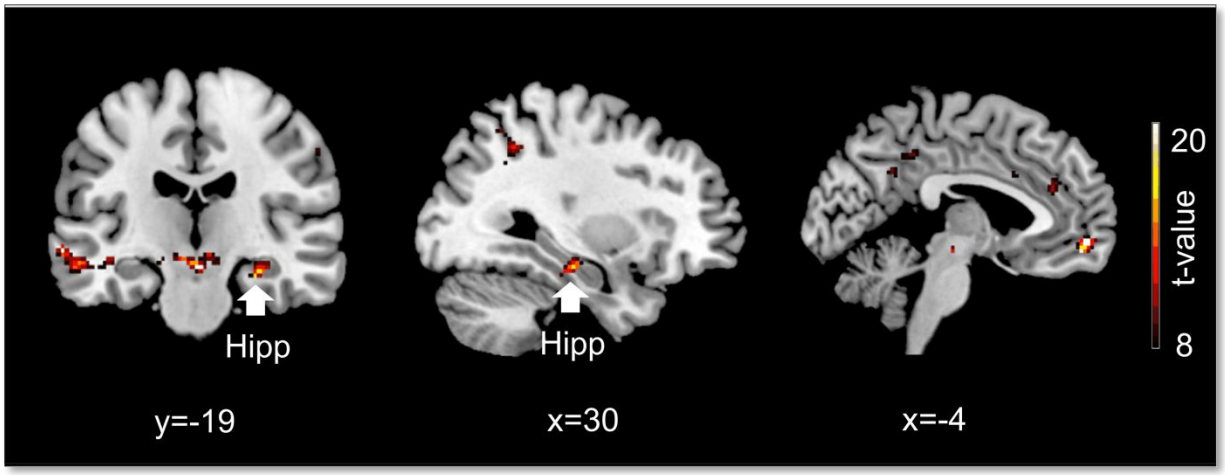


Figure 24. Main effects of the autobiographical events versus new events contrast rendered onto coronal and sagittal views. Statistical maps are thresholded at a $p < 0.05$, uncorrected at whole brain level. Hipp: R-Hippocampus.

We also visually explored the results of the same contrast for each individual at a lower statistical significance threshold ($p < 0.05$, uncorrected). This allowed us to observe that main target brain regions involved in AM recollection, such as the Hippocampus, could be seen at individual level (**Figure 25**).

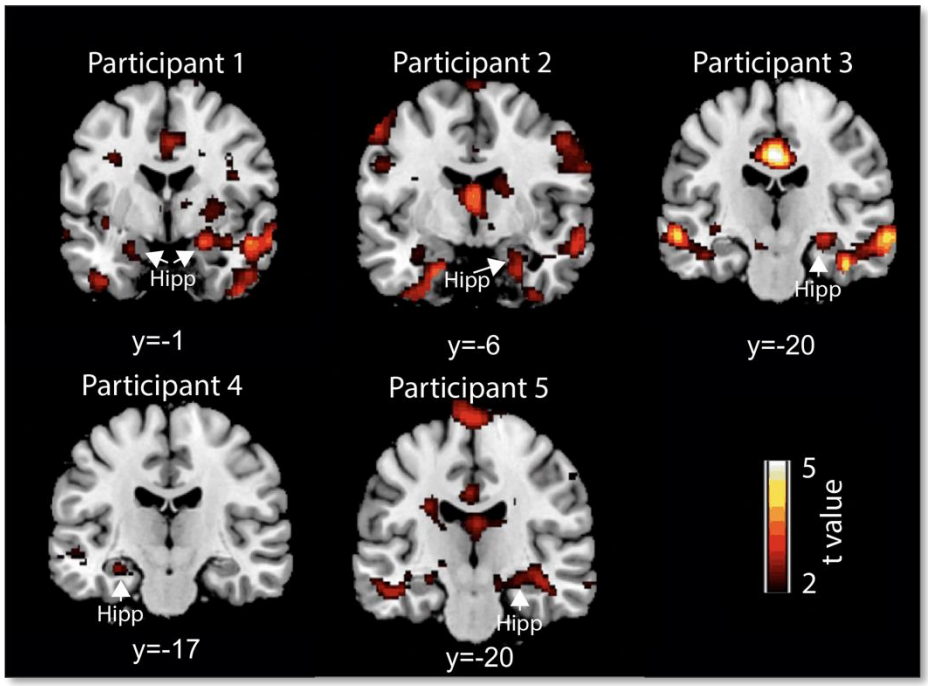


Figure 25. For exploration purposes individual activation maps rendered onto coronal views show the involvement of the hippocampus in the autobiographical events versus new events. Statistical maps are thresholded at a $p<0.05$ uncorrected, for illustrative purposes. Hipp: R- Hippocampus.

Table 3.MNI coordinates of significant fMRI activations peak clusters (p < 0.001, k >80 voxels extent).

Region	Cluster size					Group effect	
		BA	x	y	z	Z	p
R. Hippocampus	82	54	28	-18	-18	4.13	0.009
L. Orbitofrontal area	128	10	-2	52	-12	5.05	<0.001
L-Posterior temporal supramarginal Gyrus	180	39	-52	-52	16	4.48	<0.001
R. Posterior middle temporal Gyrus	97	21	38	-52	2	4.31	0.003
L. Middle temporal gyrus	300	21	-64	-20	-6	5.30	<0.001
L. Anterior cingulate Gyrus	98	32	-4	36	22	3.57	0.003
L. Posterior Cingulate Gyrus	413	31	-12	-46	32	4.19	<0.001
R. Anterior Cingulate Gyrus	82	31	0	8	22	3.69	0.009
L. Inferior Parietal Lobule	90	40	-52	-50	50	4.21	0.005
R. Inferior Parietal Lobule	441	40	48	-44	40	4.37	<0.001

Note: BA: Brodmann's area. L: Left; R: Right. p: FWE-corrected. Z: z-values

5.4 Discussion

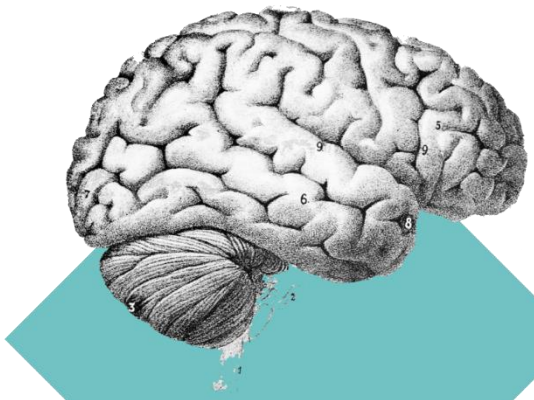
Recalling real-life AMs under ecologically valid experimental designs has been shown to be far more complex than recalling simple memories depicted in standard laboratory-based memory designs (Roediger & McDermott, 2013). AMs from real-life are thought to be complex when compared to lab-based memories, due to the engagement of its unique domain-specific processes related to re-experiencing (e.g., perceptual and emotional), and its domain-general processes (e.g., working memory and attention) required for successful retrieval (Svoboda et al., 2006). fMRI studies investigating AM with realistic material (e.g., Cabeza & St Jacques, 2007) have shown widespread brain region activation patterns, suggesting the recruitment of multiple regions during retrieval. Here, we provided preliminary evidence that such widespread brain network engagement can be elicited as well when participants' AMs for their daily life activity are cued by pictures recorded automatically with a wearable camera. Thus, these preliminary results suggest this novel experimental approach may be valid to elicit the re-experience of one's past event episodes, even at the individual level.

The current preliminary results are in line with past literature describing the engagement of three main brain networks associated to the retrieval of our personal past: a medial prefrontal cortex network (PFC), an MTL network and a frontoparietal network (St. Jacques & De Brigard, 2015). Our results showed significant activation of the orbitofrontal area and the anterior cingulate gyrus corresponding to the medial prefrontal network (PFC). The Orbitofrontal cortex is strongly

interconnected with the medial temporal lobe (Aggleton & Brown, 1999) and animal work has suggested that damage to this area impairs recognition memory (Petrides, 2000). The anterior cingulate gyrus has also been associated with the reconstruction of AMs during retrieval (Cabeza & Nyberg, 2000; Fletcher, 2001). These frontal lobe activations presented left-lateralized activations in line with other fMRI AM studies (Maguire, 2001a). Thus, the use of picture cues depicting past experiences seems to also be effective in recruiting this PFC network.

Interestingly, we found consistent hippocampal activation associated to the retrieval of AMs in our study. The role of the hippocampus in the encoding processes is well established (Spiers, Maguire, & Burgess, 2001), however, whether the hippocampus itself should be involved in the retrieval of AMs remains a matter of debate. In the poles of the controversy lies the possibility that remote AMs may have been consolidated and consequently become hippocampus-independent (according to the Systems Consolidation Theory – Diekelmann & Born, 2010), whereas other influential views suggested the involvement of the hippocampus whenever the retrieval involved specific details related to event episodic experiences, independent of its age (Multiple Trace Theory; Moscovitch et al., 2016). Our results showed right-lateralized activation of the hippocampus, although most AMs studies showed typically left-lateralized patterns (for exception see: Levine, 2004; Markowitsch, 1995). Some studies related this asymmetry of activations between AM studies to the stimulus modality used as cues, being verbal cues eliciting left hippocampus and visual cues eliciting the right hippocampus (Maguire, 2001).

In summary, the current findings provide preliminary evidence that our novel experimental approach may be suitable and effective to study how brain activity regions support the retrieval of AMs. This allows for future strategies to be developed and transfered into clinical scenarios, whereby task designs are capable of assessing behavioural and brain functioning at the individual level as required. The current approach may provide a valuable avenue to meet this challenging research and clinical milestone.



Chapter 6
General Discussion

Chapter 6: General Discussion

Although the studies included in this thesis have been discussed individually at the end of each corresponding chapter, I will hereby summarize the results and discuss them in a general manner including some additional ideas and thoughts.

6.1 Summary of Study 1

In study 1, we explored the memory integration processes that arise when combining overlapping information into relational networks. We developed a novel inferential task design that included two different conditions: associative and schematic. These conditions differed in the underlying representational nature of the overlapping elements. We hypothesized that different memory integration operations would support the integration of information into schematic networks, when compared with associative networks. We also examined the role of the hippocampus in inferential learning by exploring the generalization ability of a group of TLE patients with specific lesions at the MTL structures. Our results support the notion that neural responses and mechanisms supporting memory integration differ as a function of the underlying relational network properties. Data from TLE patients suggests that the hippocampus plays a key role in integrating information across separate events and that it supports mnemonic generalization. In the following section (**Section 6.1**), I will discuss further the nature of our findings and I will present some hypotheses regarding the role that theta oscillations play in explaining our results. I will also explain why memory reactivation may be relevant in the context of our results, and finally, I will provide reasons that support how these results can be linked to current views of memory models and how they can inform about their implementation in real life-like scenarios.

6.1.1 Building relational networks through integrative encoding

In study 1, we encouraged integrative encoding by instructing participants to learn pairs of overlapping associations through two consecutive learning phases. At the behavioural level, participants showed high accuracy (i.e. > 90 %) in learning directly experienced associations in both learning phases, a required premise for successful inference. This is a critical point, as it provides access to the elemental encoded representations when faced with novel judgments at the final inference task.

A striking finding was that higher levels of accuracy were achieved relatively rapidly at learning phase two when compared to learning phase one. This could be explained by the fact that learning

phase two requires the learning of fewer pairs of associations compared to learning one, but also, these results could be supported by the notion that this learning phase, but not the previous one, required the integration of novel elements into an existing memory network, thereby accelerating participants learning. Schema theory posited that regular patterns in the environment could be captured by abstracting information across different experiences (Bartlett, 1932), and like integrative encoding, schemas build knowledge representations from multiple individual events, representing relationships between associated elements not experienced together. Reactivating an existing schema (in this case, overlapping associations from learning phase one), could allow for rapid acquisition of new face-context associations, as has been observed in spatial learning paradigms in rodents with flavour-place associations (Tse et al., 2007, 2011), and integrate the new information directly into existing knowledge frameworks. Without an existing schema, associative learning will require repeated training across multiple blocks. Thus, the formation of relational networks via associative learning could be favoured by the presence of a prior schema. One way or another, our results confirmed that the information was successfully learned and integrated, as could be observed in the average participant's accuracy at the generalization and trained tests, administered at the end of the experimental task (see **Figure 12 B** at Chapter 3).

As stated in the introduction (see Chapter 1), building relational networks from overlapping information requires several steps. An initial encoding of elemental associations, followed by the reactivation of these associations by their overlapping elements (via pattern completion mechanisms: Rolls, 2013), which then allows to recombine all elements into an integrated memory representation. In study 1, we promoted the creation of two different relational networks based on the nature of their underlying overlapping elements: either associative or schematic conditions. We hypothesized that the formation of these mnemonic structure representations through consecutive learning phases would be different at the schematic condition compared to the associative condition (see the proposed network models in **Figure 11 D** and **E** in Chapter 3). We speculated that the reason for these differences is related to the different levels of processing and mnemonic hierarchies that must be covered in the schematic network when integrating a new item.

6.1.2 What is the role of theta oscillations in schematic relational networks?

Our neurophysiological results showed differences in the electrophysiological mechanisms that underlie memory integration when compared associative condition to schematic condition. In order to explore this, we centred our analysis on a low-frequency oscillation found in the hippocampal local field potential called *Theta rhythm*, that has been related to learning and

memory (see Theta oscillations at encoding and at retrieval at Chapter 1). Although this neural oscillatory activity has traditionally been related within a range of 4-8Hz in humans and 6-10Hz in rodents, recent human studies have reported findings at the lower end of the traditional band in spatial and temporal contexts (Jacobs, 2014; Watrous et al., 2013) and in memory integration processes (Backus et al., 2016; Sans-Dublanc et al., 2017). For this reason, we targeted our analysis at the 3-6 Hz range, and our results confirmed the hypothesis that theta power was prolonged in time when integrating novel elements into existing schematic memory networks compared to when integrating novel elements into associative memory networks.

This leads to the question of what the role of theta oscillations during memory integration in schematic memory networks is. Evidence has related theta oscillations to the firing of place cells representing the animal's position in space (Ekstrom et al., 2005; Jacobs et al., 2013) or successful navigation and spatial memory encoding in humans (Kaplan et al., 2012; Miller et al., 2018). Recent studies have, however, suggested that theta power may be correlated with spatial distances (Herweg et al., 2018; Vass et al., 2016). Although other studies have tried to link spatial and episodic associations during encoding (Buzsáki, 2005; Kumaran & Maguire, 2005), little is known about the potential shared role of theta mechanisms in these two different domains.

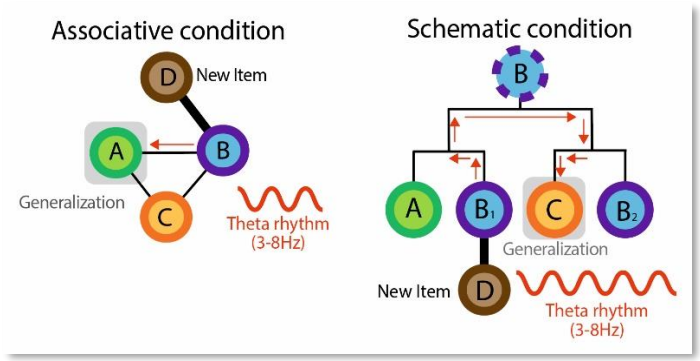


Figure 26. Learning phase two in **Study 1**. Proposed network model for associative and schematic condition signalled by theta oscillations.

Solomon et al., 2019, asked if hippocampal theta oscillations represented semantic distances between words, similar to how these oscillations coded for relationships in physical space. In that study, patients with depth hippocampal electrodes completed a study and a memory test phase of lists of items encoded during the study phase. During the test, patients showed behavioural patterns of clustering the items of the list based on temporal relationships and on semantic relations. Solomon et al., 2019 proposed that theta oscillations indeed reflected representational distances between word-items in memory. Our results also pointed in this direction, considering

the theta power extended longer in time when new items were integrated into an existing schematic memory network compared to when they had to be integrated into an associative memory network (see **Figure 13** in Chapter 3). We speculated that this difference in length could be explained by a search process led by theta oscillations when exploring the relational network space, that could have a wider distribution in the schematic condition and would be connected through hypothetical conceptual nodes (e.g., landmarks or people) and edges (e.g., roads or social connections). This extended view of the role of theta would be in line with central ideas sparked by the Spreading Activation Theory (Collins & Loftus, 1975). This theoretical framework posited that the activation of a conceptual node spreads to the adjacent network nodes, representing other but related conceptual nodes. Thus, theta oscillations may, speculatively, reflect the automatic process of activation spread throughout a relational and schematic network.

One could say that the differences in theta power between conditions may be explained due to the differences in the difficulty between conditions in the task. However, this seems an unlikely possibility given that learning phase 2, where we found theta differences, requires participants to encode exactly the same type of elements and relations between them (see **Figure 12 B** in Chapter 3). Another possible interpretation would be that the extra number of associations linked to the schematic condition in phase 1 requires higher cognitive load during new learning in phase 2. However, studies have shown that theta power may in fact decrease with memory load (Brzezicka et al., 2018) and other studies were unable to find changes in theta due to cognitive load (Cummins, Broughton, & Finnigan, 2008).

6.1.3 Is the hippocampus engaged in relational memory networks?

Along with the hippocampal theta results we aimed to investigate if the hippocampus was necessary for memory integration. According to recent findings (see Chapter 1), the hippocampus is involved in creating and maintaining spatial maps of our environment. The relational theory suggests, however, that the hippocampus is involved in relational memory processing, or in other words, in establishing relational links between separated elements of our experience (Eichenbaum, 2004). Furthermore, the amount of relational processing has also been found to modulate hippocampal activity (Cohen et al., 1999). In study 1, we examined a sample of fourteen participants with refractory temporal lobe epilepsy (TLE) and damage to the right or left medial temporal lobe structures including the hippocampus. Our results showed that patients were able to learn individual associations during the task, showing consistent above chance performance with no differences between conditions (see behavioural results of the trained test of patients in **Figure 15B**). However, at the generalization test, patients showed a poor ability to generalize in

both conditions (i.e., they were at chance) compared to controls. These findings suggest that in some way, the hippocampus is critical to memory integration, thereby lending support to previous fMRI findings that documented an increase in hippocampal activity during inferential tasks (Preston & Eichenbaum, 2013; Schlichting & Preston, 2015; Zeithamova et al., 2012).

Overall, nowadays, there is a general consensus of the critical contribution of the hippocampus in episodic memory (Scoville & Milner, 1957; Squire, Wixted, & Clark, 2007; Tulving, 2001). The hippocampus is known for rapidly bind representations of elements together during memory integration, however, how can this binding occur for elements within a schematic memory network? As stated previously, we suggest that the process of memory integration for schematic representations may take longer than for associative representations due to the representational distance required to reach other representations within a schematic network. In line with this hypothesis, Cutler, Duff, & Polyn, 2019 proposed a relational search hypothesis. They explained that a single concept is represented at the neocortex as a network, with nodes and edges representing the relationships within related features between this network. When a concept label arrives, these feature representations are activated in the neocortex but also, at the same time, in the hippocampus. In the hippocampus, all these features are bound, creating a hippocampal representation of these elements more fully connected than those in the cortex, and also less sensitive to graded levels of feature association. The cortical activation of one concept feature would activate the conjunctive code at the hippocampus, and the other related features could be retrieved via pattern completion (see introduction Chapter 1). This representational structure at the hippocampus enables activating distant features more easily when compared to cortical representations alone (Solomon & Schapiro, 2020). Patients with hippocampal damage would have restricted movement through the memory space, losing the advantages in searching given by the hippocampus, and making searching throughout distributed representations at the neocortex more complex.

6.1.4 Hippocampus – Prefrontal Cortex interactions in schematic memory networks

Theta rhythms have also been related to the coordination of hippocampal-prefrontal cortex (PFC) activity (Jones & Wilson, 2005). The theta synchrony between hippocampus-PFC activity constitutes a general mechanism through which the timing of disparate neural activities can be controlled, allowing the transfer of information between the two neural structures according to current behavioural demands (Jones & Wilson, 2005). Based on this evidence, our theta findings

could also inform about the engaging of a long-range network connecting different structures aside from the hippocampus.

The PFC is a central structure in generalization processes. Indeed, it has been shown that vmPFC activity and its connectivity with the hippocampus correlates with subsequent generalization performance (Zeithamova et al., 2012a; Zeithamova & Preston, 2010). One model proposes that the vmPFC reactivates schemas when they are consistent with incoming information and also when integrating new information into these schemas (Van Kesteren et al., 2012). Other studies proposed that the hippocampus is responsible for supporting individual memory associations and the PFC is engaged only when the relational processing is needed (Christoff et al., 2001). Another hypothesis posited that the hippocampus, apart from the PFC, also contributes to this relational processing (Hannula & Ranganath, 2008; Hannula, Tranel, & Cohen, 2006).

In addition, the PFC engages in operations that guide, organize, and/or modify representations maintained by other regions. mPFC is thought to form memory models (St. Jacques, Olm, & Schacter, 2013) that bias hippocampus retrieval towards task-relevant memories (Preston & Eichenbaum, 2013). The PFC in addition could provide top-down modulation of representations in the visual cortex (e.g. enhancing attention to valuable information and suppressing information that has to be ignored; (Gazzaley et al., 2005) and also when retrieving information to reduce reactivation of irrelevant information (Kuhl, Bainbridge, & Chun, 2012). The vmPFC, as stated in the introduction (see Chapter 1), receives direct input from the hippocampus and also has extensive connections with sensory, limbic and subcortical structures (Cavada, 2000). This pattern of connectivity suggests that this structure may be essential for integrating information from distributed cortical and subcortical networks. Patients with lesions at the vmPFC appear to have deficits in creating and using abstract representations to guide behaviour, suggesting that abstract representations or schemas, are stored in this region and are continually shaped, updated and modified via hippocampal - PFC interactions within the intact brain (DeVito et al., 2010; Iordanova et al., 2007; Rubin, et al., 2017). In fact, the activity of theta phase-locked neurons in the prefrontal neurons is correlated to task representations and the exchange of information within the hippocampus in rodents (Hyman et al., 2005). Focussing on the extended theta power observed at schematic neural networks in our study, one explanation of our results could be that theta power on schematic representations, at searching and updating target information in the prefrontal cortex, need extended hippocampal – prefrontal communication; as the representations in the prefrontal cortex are wider spread compared to the associative condition.

6.1.5 Memory reactivation in memory integration

As forementioned in the previous section, the hippocampus and the PFC support flexible memory processing by allowing the combination of related memories and using it in novel ways. Memory updating relies on the process of reactivation, or the activation of a latent memory trace when we are reminded of a past experience, shaping long-term memory representations by organizing them through memory networks (Zeithamova et al., 2012a). The simultaneous activation of representations of novel inputs and past reactivated memories that overlap in content promotes integration and storage into long-term memory, thereby promoting updating. Therefore, it is reasonable to assume that the quality of the reactivated memory may modulate integrative encoding. In study 1, we used neural similarity analysis to measure how similar two neural patterns were for events that were encoded separately in time but shared partial information (see **Figure 14 A and B**). We observed that the temporal dynamics of memory reactivation depended on the typology of the underlying neural network and that this reactivation, during memory integration, seemed to adapt according to the structural properties of the mnemonic network. Specifically, we found greater pattern similarity for elements within associative memory networks rather than for those within schematic networks (see **Figure 14 A**). We hypothesized that memory reactivation mechanisms were differently engaged in these two conditions as a result of a regulatory principle that promoted links from direct associations only. This regulatory mechanism would be important to prevent continuous reactivation when the representation of an event in memory shares elements with the current experience. We suggested that when the associated events are found in our memory space, these memory representations would be fully reactivated and integrated into the network (e.g. associative case), but when these representations were not found rapidly, higher levels of memory representation are engaged increasing the chances of finding a related memory (e.g. schematic case).

Given the strong reliance of memory reactivation in integrative encoding, we hypothesized that the inability of TLE patients to generalize could, at least partially, be explained by hippocampal-dependent deficits in triggering memory reactivation. Indeed, hippocampally-mediated reactivation of prior experience during the encoding of new overlapping events was associated with greater later retention (Kuhl et al., 2010). One possibility is that a deficit in hippocampal-mediating reactivation mechanisms in the TLE patients caused the reactivation of conflicting memory representations that compete with the relevant ones, preventing the update of correct associations and the correct schema of each situation (Kuhl et al., 2012). The negative influence that competition has on memory has been found to decrease the probability of retrieval success and reaction time (Anderson, 1983) preventing the spreading activation through the network

(Collins & Loftus, 1975) and failing in the searching process. Unfortunately, our experimental task was designed to limit participants to respond quickly, in this way we would be capable to explore EEG data during picture cues without motor artefacts in the signal. This, however, came with the downsides of not being able to evaluate reaction times between conditions to corroborate this claim.

6.1.6 Concluding remarks

Building relational networks is a process that we perform in our everyday lives. For instance, we meet someone new at the laboratory talking with a PI and then attending the seminar, and we could infer, that he/she is a new student of brainvitge. This process of integrating overlapping information based on the repetition of context or people is useful to rapidly integrate new information and explain what is happening around us, however, this may come at the cost of the degree of detail in which we remember past experiences from our everyday life routine activity, as detailed below.

6.2 Summary of Study 2 & Study 3

We experience our lives in a stream of routine activity and goal-related experiences. To achieve future goals, it is essential to have a record of how one has progressed with the same or related goals in the past. In order to remember very recent goals such as whether we have locked the car, what we had for breakfast, or even how we commute from one place to another, the revision of these daily activities leads us to rapidly check whether these goal-related actions have been executed correctly. Many of these routine activities are not self-relevant and, consequently, may not necessarily need to be remembered in the long-term. However, many other activities are integrated into our autobiographical memory and are highly associated with the experience of remembering. In study 2 and study 3, we asked participants to record pictures depicting daily life activities through a wearable camera for a period of one week. From this camera, we extracted many sequences of photographs that together constituted multiple events representing the participant's life. In study 2, we organized these events through a segmentation algorithm (see Chapter 4) and we selected one photograph from each event, in order to generate valid cues that elicited the retrieval of the experienced event by each of the participants. We developed a protocol that allowed us to evaluate 1) whether the cues were powerful enough to evoke the retrieval of experiences, 2) the effectivity of the protocol to study, at individual level, neural mechanisms that underlie the retrieval of autobiographical memories, 3) the quality of the memories recollected

and finally 4) the effect that the passage of time has on our memory representations. In study 3, we applied this protocol to a small sample of healthy adults and studied the brain sources that supported retrieval through functional Magnetic resonance imaging (fMRI).

6.2.1 Validating the experimental protocol

Our behavioural results suggested that picture cues were effective in eliciting the retrieval of AMs as participants showed high levels of accuracy in all memory tests. We confirmed that these high recognition values were not due to emotional factors as the participants tended to respond that their retrieval was accompanied by neutral emotions. We could observe from our neurophysiological data (i.e., ERP results) that picture cues depicting one's personal past triggered a clear and statistically solid differential neural response compared to picture cues depicting another participants' past. In study 3, the same protocol was applied during fMRI scanning and we found that the same contrast showed the engagement of a core autobiographical memory retrieval network. Altogether, our findings lend support to the conclusion that this novel experimental approach to explore real-life AMs at the individual level is valid and may be suitable for implementation in clinical studies that have an important focus on single cases.

6.2.2 Real-life versus laboratory-based experimental designs to study AM

As stated in the introduction section of the thesis (see Chapter 1), there is a current debate about whether the study of AMs through the use of lab-based or ecologically valid and naturalistic material capture the same or different retrieval memory processes. Some studies have found differences in the neurocognitive processes supporting performance on laboratory measures (Gilboa et al., 2004; McDermott et al., 2009), while others reflect limitations in the existing experimental paradigms (St. Jacques, Rubin, & Cabeza, 2012).

In study 2, participants were also asked to encode lab-based material that mimicked scene pictures depicting real-life scenarios (e.g., common indoor and outdoor daily-life contexts; see Chapter 4 for details). One week after encoding, participants returned to the lab and performed a recognition memory test of that encoded material. We then compared the participants' accuracy for each of the memory tests and observed that their accuracy to memories with lab-based material decreased significantly, thereby suggesting that the encoding of lab-based material lacks the easiness that seems to underly the encoding of real-life experiences.

Although participants did achieve higher levels of accuracy at the recognition memory test for real-life material, their results were slightly different when we evaluated their confidence ratings.

The highest rated option, on average, was the 'know' option. This explains that participants could recognize the autobiographical cues as a part of their routines, although they could not remember vividly what happened before and after these events. These familiarity responses were higher on average when compared to recollection responses, but recollection ratings showed that participants still retained some vivid details about the data-collection week. At the lab-test, although recognition memory was maintained, confidence ratings showed a different pattern. Guess responses were the highest rated option between participants followed by familiarity responses that were lower than Guess responses. Recollection responses on this test were on average anecdotical. This indicates that retaining details about the scenes depicted in the lab-based experiment was difficult for the participants, and that recognition memory could be associated with different subjective experiences in lab-based studies compared to real-life studies.

When we compared the neurophysiological responses, we observe that lab-based ERPs did show the expected *old/new effects,* but the degree of these effects was not as large as that the ones we had clearly observed through the AM test. This could be interpreted, as previous studies have (King et al., 2005), as the participants encountered greater contextual interferences at the lab-based test, resulting from a large number of events encoded in a limited context (in front of the computer), compared to the autobiographical experience in which contexts were richer and more distinct. Our results support the view of autobiographical memory traditions that highlight the complexity of autobiographical events, likely different from lab-based events that tend to be more passive and less self-related (Cabeza et al., 2004), and recognize their richness and their personal relevance for the participants.

6.2.3 How autobiographical memories change over time

In study 2, recognition memory was tested at three different points in time: one week (T1), two weeks (T2) and from 6 months to 1 year (FU) from encoding. Although recognition memory accuracy was highly maintained during the three tests, we observed a significant reduction in the accuracy values between T1 and FU tests. This confirms that our experimental approach was capable of capturing the notion that the passage of time involves some degree of forgetting or representational transformation, even for memories of real-life experiences. Thus, some theories posit that the quality of memories undergoes transformations due to consolidation, going from initially context-bound memories to a schematic version because of time and repeated experience (Winocur, Moscovitch, & Bontempi, 2010). Alternatively, the loss of memory details over time could be explained by the inherent forgetting processes over the passage of time for events that

may not be meaningful or salient enough to be integrated into the autobiographical representations.

The remoteness effect observed in real-life memories relates to another important debate regarding the role of MTL structures, especially the hippocampus, in episodic memory. The standard model of consolidation predicts no activation of the hippocampus for remote memories (Alvarez & Squire, 1994), whereas the Multiple Trace Theory (MTT) (Nadel et al., 2000) states that episodic memories are always supported by the connections between the neocortex and the hippocampus, regardless of the age of memories. According to the latter, the reactivation of a memory trace leads to the creation of a newly encoded hippocampal trace. Over time older memories would be associated with large number of memory traces because of the probability of being rehearsed (Nadel & Moscovitch, 1997). One of the reasons why this debate still persists is because it is difficult to disambiguate it empirically in humans, as real-life activity tends to have a high degree of overlap and therefore it makes complicate to assess whether specific event memory is genuinely preserved or not over time. Our preliminary fMRI findings from study 3 support the MTT as we found consistent hippocampal involvement during the retrieval of real-life AMs. However, retrieval accounted for memories that ocurred 1 week from encoding, this is still insuficient to allow a memory to be fully consolidated in humans. In addition, some studies have shown greater activation or different distribution of activations within MTL for remote memories compared to recent memories (Gilboa et al., 2004), although other studies were unable to find them (Steinvorth et al., 2006), or found other neocortical areas such as the prefrontal cortex during recent memories and decreasing activity as memories become remote (Maguire, 2001a). Previous studies have shown that the hippocampus remains involved in remote autobiographical memories as long as they remain vivid and detailed (Addis et al., 2004; Sheldon & Levine, 2013). Thus, this debate remains open and future studies combining neuroimaging techniques, real-life material and different temporal gradients between encoding and retrieval may help clarify this key issue.

Nevertheless, we believe that our theta results from study 2 may contribute to this debate. As stated in the introduction (see Chapter 1), neural oscillations may be a mechanism by which widespread regions communicate during memory retrieval. Theta oscillations have been shown to mediate MTL-neocortical communication during retrieval (Battaglia et al., 2011) and theta phase coherence between these regions has been identified in spatial (Kaplan et al., 2017) and autobiographical memory (Foster et al., 2013). Thus, we speculate that finding theta activity during the retrieval of each of these memory tests, may indicate the engagement of the MTL-neocortical network and, consequently suggests the participation of the hippocampus during the

retrieval of memories at one week but also at one year after encoding, which would agree with the MTT. Overall, we need to be cautious about how we interpret the effects of "remoteness" in AMs. As described in the Introduction section of the thesis (see Chapter 1), several factors modulate hippocampal activity during retrieval. For instance, the hippocampal activity could reflect re-encoding processes as a result of the incidental encoding during the evaluation of the cue; or to consider that memories from different time periods would differ not only in age but also in other factors such as vividness or accessibility (St. Jacques et al., 2013).

Another controversial issue refers to the fact that theta power modulation has been seen in the literature as either an increase or a decrease. For instance, several studies have found increases in theta power for correctly remembered items compared to new items (Düzel et al., 2003; Klimesch et al., 2000; Klimesch et al., 2001; Mormann et al., 2005; Osipova et al., 2006). Other studies have related the successful encoding or spatial processing with an increase of theta power and MTL activity in tasks that involved a certain degree of reactivation (Backus et al., 2016; Kaplan et al., 2012; Sans-Dublanc et al., 2017). However, some other studies found theta power decrease in association with successful memory encoding (Burke et al., 2013; Fellner et al., 2016; Greenberg et al., 2015; Long, Burke, & Kahana, 2014). Our findings that theta power decreased during the retrieval of AM memories could also be linked, as some studies have proposed (Staudigl, Hanslmayr, & Bäuml, 2010), to a successful interference resolution via inhibition. Searching for the past could lead to the reactivation of relevant and irrelevant memories according to the multiple and related event-cues presented during the experiment.

6.2.4 Concluding remarks

The retrieval of AMs involves complex processes that include the retrieval of semantic representations, personal significance attribution, subjective re-experiencing, the retrieval of spatiotemporal contexts, emotions and social interactions and varying levels of specificity, remoteness, and rehearsal (St. Jacques & De Brigard, 2015). Thus, studying the cognitive and neural underpinnings of mechanisms of AMs is difficult and an effort to develop useful experimental designs is needed. In this thesis, we have provided a new experimental protocol that could deepen our understanding of how neural activity relates to conscious autobiographical memory experiencing (Study 2) and its underlying brain sources (Study 3). Thus far, most of the existing behavioural and neuroimaging studies have used laboratory stimuli (e.g., words or pictures) to test memory. These studies have clearly contributed to a deeper understanding of episodic memory. However, one of the downsides is that the stimuli lack the richness and relevance that are associated with the learned material during our day to day life activity, which

could eventually lead to the activation of different neural networks (Roediger & McDermott, 2013). We have contributed to the comparison between lab-based/autobiographical methods by finding differences during the retrieval of these two types of stimuli (Study 2), leading to the question of whether we are measuring distinct or the same type of memories.

A model that is useful to understand this complexity is the Self-Memory System (SMS) (Conway & Pleydell-Pearce, 2000). The SMS is considered to be a virtual memory system that consists of a temporary interaction between control or executive processing systems with a multi-layered long-term memory knowledge base (Williams & Conway, 2008). The executive aspects of the systems are termed *the working self* and consist of current active goals, the conceptual self (beliefs, evaluations) and past, present and future self-images. In this model, the *working-self* modulates memory by exerting control access to the cues used to activate the *autobiographical memory knowledge base*. This is achieved by a fine-tuning the cue, several times, so that particular types of information are activated. According to this model, long-term memory contains two types of autobiographical representations: *autobiographical knowledge* and *episodic memory*. Autobiographical knowledge is hierarchically organized from highly abstract (conceptual self), to event-specific and experience near (episodic memories) (**Figure 27**).

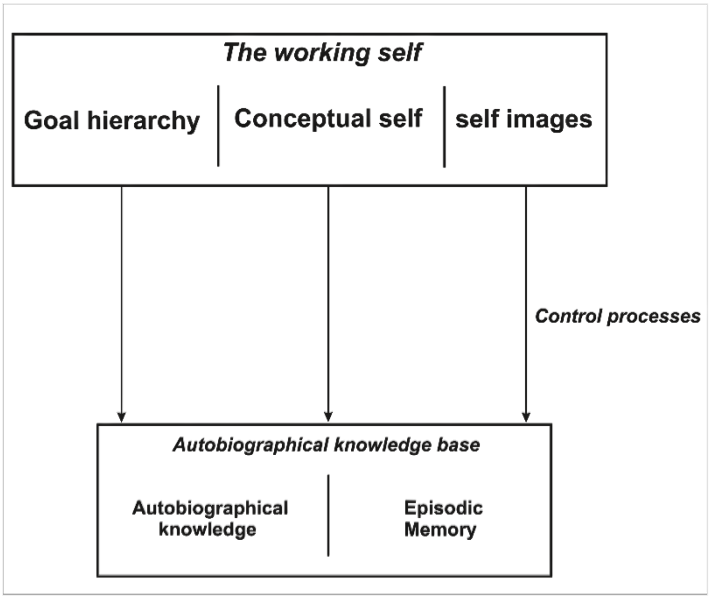


Figure 27. Relationship between the working self and the autobiographical knowledge. Adapted from Williams & Conway, 2008.

Inside the *conceptual self* (see **Figure 28**), *lifetime periods* play an important role in the organization of memories and could act as life story schema supporting the generation of themes (e.g. my work environment schema). *General events*, on the other hand, are part of the knowledge

base itself and have been found to play important roles in organizing personal knowledge. General events are more event-specific than lifetime periods but not as specific as sensory-perceptual episodic memories, derived from actual experience. Therefore, autobiographical memory consists of autobiographical knowledge and episodic memories.

Episodic memory is highly event-related and consists of detailed records of sensory-perceptual and conceptual-affective processing that were prominent during the original experience. They are predominantly visual in nature and represent short time-slices of experience related to the moment-by-moment segmentation of experience into events (Zacks & Swallow, 2007). Many episodic memories will be formed every day and going back over the events of a day, will bring to mind many highly detailed and specific episodic memories of events that occurred earlier that day. Conway, 2005 argues that episodic memory is the memory system that keeps a record of every recent-goal related activity and facilitates short-term goal processing. However, as time passes and the retrieval interval increases, many of these episodic memories that are not self-relevant or routine events become inaccessible. It has been suggested that only those memories that are linked to currently active goals become integrated with autobiographical knowledge in long-term memory. Episodic memories integrated in this way are retained over long retention intervals (months, years, decades and even a lifetime).

Relative to the initial question of whether autobiographical and episodic memories are distinct or the same, we could re-interpret our autobiographical sampling (Study 2 and study 3) focussing on the SMS theory. We could hypothesize that over time, we are measuring different memory systems. In the T1 test, one week after the data collection, we could be measuring episodic memory, as the participants could still recall recent-goal related routines with high accuracy and a certain degree of detail. As time passes (FU test: 6 months to one year after data collection), participants' accuracy decreases significantly, and also detailed memory, indicating that routine events that were not self-relevant to the participants were not incorporated into the autobiographical memories. We could not find changes in the electrophysiological responses or in the theta oscillations over time, despite the fact that several theories have posited that the hippocampus has a role in vivid autobiographical memories in perpetuity (Nadel & Moscovitch, 1997; Winocur & Moscovitch, 2011). Perhaps because neurophysiological methods, such as EEG, are not able to capture the underlying networks that support changes in autobiographical memories, or because, as some studies pinpointed (Maguire et al., 2001), consolidation processes could decrease power making it difficult to capture these effects.

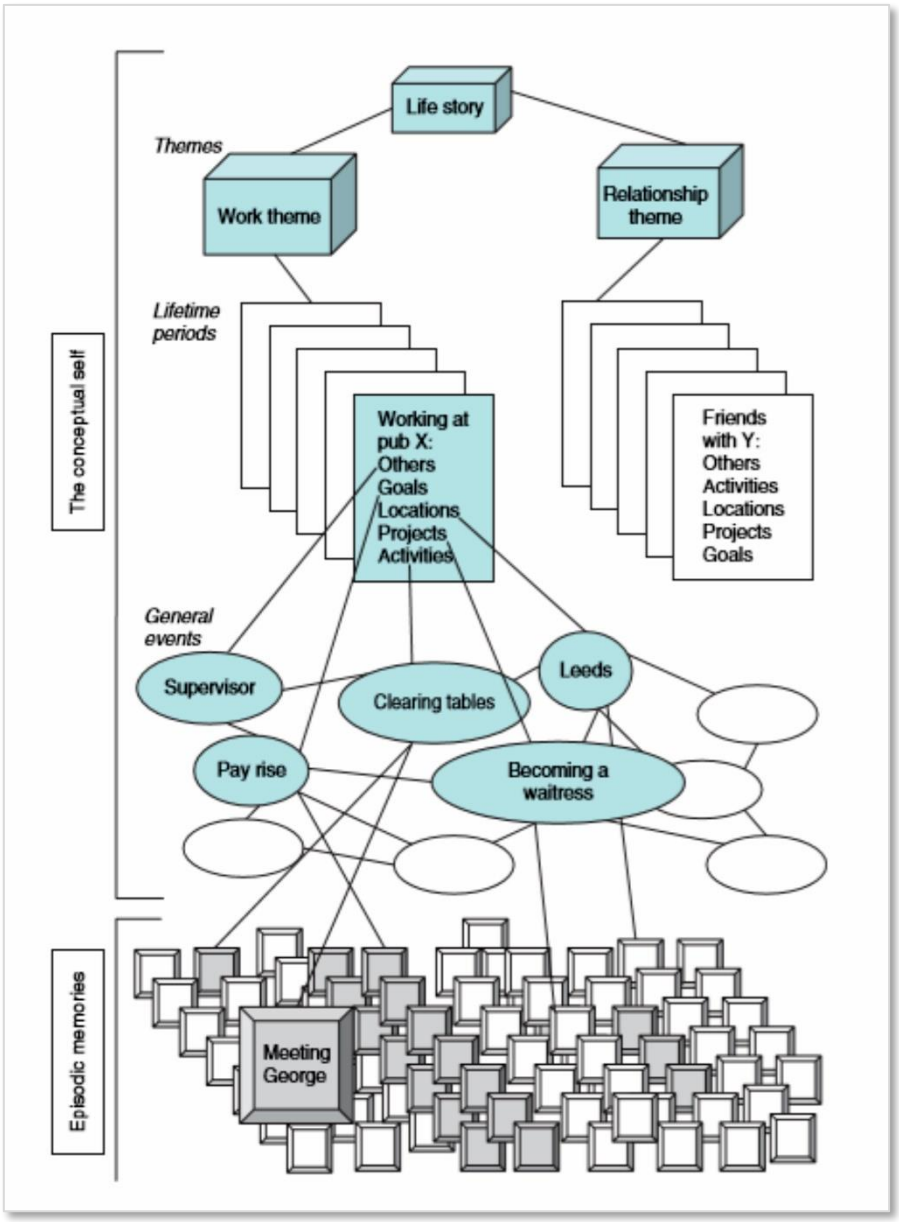
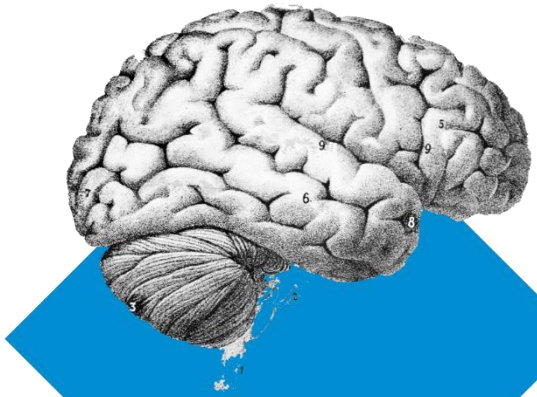


Figure 28. Knowledge structures in autobiographical memory. Adapted from Williams & Conway, 2008.

Regarding the relationship between encoding and retrieval processes linking study 1 with study 2, we could observe different dynamics of theta oscillations responses during integrative encoding and retrieval. In study 1, during memory integration of episodic events, theta oscillations increased in the 500-1500 ms time window. On the other hand, theta oscillations decreased from approximately 1200 ms to the end of the time window during the retrieval of the event-episodic memories. These results suggest that theta oscillations may have different roles during the integration and elaboration of memories. We speculated that theta oscillations as an efficient regulatory mechanism that supports, during integrative encoding, the integration and organisation of interlinked information into relational memories (see **Figure 28**). On the other

hand, retrieving a specific autobiographical episode involves searching through autobiographical general knowledge (construction of the memory), and then reliving the episode vividly by accessing episodic elements (elaboration of the memory). Theta oscillations could be the regulatory mechanism that search the appropriate event-cue in the autobiographical memory knowledge base (Study 1), taking more time to find the schematic representations that are broadly organised, while dealing with the interference of related events (as indicated by the theta decrease; Study 2), when other routinely-familiar-event memories are competing in the network when compared to never seen events.

The fact that theta effects are widespread in study 2 suggests that the retrieval of AMs is supported by a different set of regions (Conway, 2005). Hippocampal-neocortical networks support the encoding and retrieval of episodic memories, lending support to the idea that the hippocampus forms links between neocortical brain regions that are necessary for contextually rich memory processing (Teyler & Rudy, 2007). Study 1 also showed that the hippocampus was central in relational memory processing of overlapping representations, as TLE patients performed at a chance level at the inference test. It remains to be explored whether different encoding and retrieval-based roles can be attributed along the longitudinal hippocampal axis. Recent interest in neuroscience has been focused on determining the nature of the physiological and structural differences existing along the longitudinal axes in the hippocampus and how this is related to behavior (Strange et al., 2014). One plausible explanation is that neural mechanisms mediating encoding and retrieval, such as pattern separation and pattern completion were distributed along this hippocampal axes (e.g., Poppenk et al., 2013), giving rise to the possibility that part of the neurophysiological measures obtained in our studies reflect similar features (i.e., theta rhythm) while expressing different behaviors (i., theta power increase and decrease).



Chapter 7

General Conclusions and limitations

Chapter 7: General Conclusions and limitations

Many judgments or decisions that we perform every day are not only based in direct experience but rather require inference. An important factor that contributes to this process is the assumption that memory representations have an overlapping nature and that this creates a structure of interlinked set of complex memory episode representations that engage specific neural mechanisms that can be studied at the lab.

In study 1, we wanted to explore how our stored knowledge could influence the formation of new memories at the time we integrate novel inputs that overlap with these existing structures. Therefore, we designed a novel paradigm that allowed us to test these integration mechanisms, while being monitored with EEG, when two different mnemonic networks are formed: one associative and one more schematic. We hypothesized that different mechanisms would subserve the integration of elements into these memory networks due to their different structural nature. Our neurophysiological results sustained this hypothesis showing that theta power was prolonged in time when integrating novel elements into existing schematic memory networks when compared to associative memory networks. Moreover, previous studies have suggested that theta oscillations could have a role on representing distances between elements in a memory network. Thus, we speculated and concluded that, in our design, theta could lead a search process through the relational network space, that is prolonged in the schematic condition, due to the representational distance required to reach the correct element within the network.

As the hippocampus is known to be the central structure that establishes links between separate elements of our experience, in study 1 we also examined, behaviourally, a sample of participants with temporal lobe epilepsy (TLE) while they were performing the inferential task. Our results showed that participants were able to retain the individual associations but failed at generalizing the information learned through the task. We concluded that the hippocampus is critical to memory integration processes because it allows the representation of relationships between the elements within a network.

The simultaneous activation of representations of novel inputs and past reactivated memories that overlap in content promotes integration and storage into long-term memory, thereby promoting updating. Throughout our similarity analysis, we observed that the temporal dynamics of memory reactivation depended on the typology of the underlying neural network and that this reactivation, during memory integration, seemed to adapt according to the structural properties of the mnemonic network. We concluded that when the associated events are found in our

memory space, these memory representations would be fully reactivated and integrated into the network (e.g. associative case), but when these representations were not found rapidly, higher levels of memory representation are engaged increasing the chances of finding a related memory (e.g. schematic case).

The process of integrating overlapping information based on the repetition of context or people is useful to rapidly integrate new information and explain what is happening around us, however, this may come at the cost of the degree of detail in which we remember past experiences from our everyday life routine activity, as we have explored in study 2 and study 3.

In study 2, we asked participants to record pictures depicting daily life activities with a wearable camera for a period of one week. We developed an experimental protocol that allowed us to test participants' retrieval of their individual and real-life autobiographical episodes. This novel paradigm permitted us to explore, at the individual level with EEG techniques, the neural mechanisms that underlie the retrieval of autobiographical memories. We could also evaluate the passage of time by testing participants at three different time periods from encoding, that included recent and remote memories. In study 3, we used fMRI and a sample of controls from a preliminary TLE patient study that is still ongoing, to assess how effective was our novel approach to engage known brain regions related to the retrieval of autobiographical memories in lab-based designs.

Based on our neurophysiological results, we conclude that our novel paradigm is a valid approach to explore real-life autobiographical memories as the pictures cues depicting one's personal past triggered a clear and statistically solid differential neural response compared to picture cues depicting another participants' past. Based on our behavioural results, we concluded that although participants could recognize the autobiographical cues as a part of their routines, it came as a cost of the degree of detail reducing the vividness of their memories. When we compared the accuracy at recognition lab-based material to the recognition of autobiographical events, our results suggested that the encoding of lab-based material lacks the easiness that seems to underly the encoding of real-life experiences.

Although recognition memory accuracy was highly maintained during the three tests, we observed a reduction in accuracy between more recent and remote time periods. This confirmed that our experimental approach was capable of capturing the notion that the passage of time involves some degree of forgetting, even for memories of real-life experiences.

Related to the ongoing debate about the remoteness effect in real-life memories regarding the role of MTL structures, our preliminary fMRI findings from study 3 supported the notion that the

connections between neocortex and the hippocampus are maintained regardless of the age of a memory. This suggests consistent hippocampal involvement during the retrieval of real-life AMs, lending support to the idea that the hippocampus forms links between neocortical brain regions that are necessary for contextually rich memory processing, and as observed at study 1, is a central structure in relational memory processing.

I hope that these studies and ideas could shed more light on the understanding of the complexity of the mechanisms that govern human memory and amaze us of all that is still unknown and is yet to come.

Limitations

The main results discussed in this chapter have contributed to expand previous knowledge regarding the encoding and the retrieval of autobiographical memories. They have provided knowledge on the neural mechanisms that support the organization of structures of information when integrating new overlapping memories and have presented a new approach to contribute to the understanding of the retrieval of personal events. While we were able to address most of the research questions, there are still some aspects to be resolved:

-In study 1 we set out to investigate the differences in the integration mechanisms between a purely associative memory network (associative condition) and a more hierarchically organized network (schematic condition). In the current study we labelled schematic memory as a set of complex interrelated picture association networks that rely on representational units that lack a unit of detail, as their elements are interrelated via semantic concepts allowing the integration of new elements hierarchically organized. Although we believe these network properties deemed for a qualitative difference with purely associative memory networks, arguably, some of them lacked a full empirical assessment in our experimental design. Previous research studies have used schema representations (Van Kesteren et al., 2012), prototypes (Bowman & Zeithamova, 2018) or linking related memories into an integrated representation (Schlichting & Preston, 2015), in this study we extended the standard AB-AC inference paradigm to more complex links proposing a novel option that has never been tested with a set of semantic concepts that would bring hierarchy into a memory network. As this notion is well established in psychological models of memory representation (Collins & Loftus, 1975), it would be important to determine the extent to which participants activate purely conceptual memory representations during learning throughout our experiment (e.g. by the use of a debriefing at the end of the experiment).

-Regarding EEG theta effects (experiment 1), it is also important to determine the extent to which the decrease in generalization performance seen in the schematic condition cannot be, at least partially, attributed to an increase of interference driven by the need to integrate more associations in schematic than in associative memory networks. The study of reaction time patterns in participant's responses during learning would have helped inform this possibility (i.e. longer RTs to trials from schematic rather than from associative condition in LP2). However, to exclude possible differences between conditions in the temporal evolution of specific neural responses recorded from scalp EEG recordings that could be attributed artefactual signals derived from motor preparation and response, participants were required to respond within the temporal window of interest (i.e. while encoded pictures were present on the screen for 3 seconds).

-In study 1 (Experiment 2) we collected a sample of 14 mesial temporal lobe epilepsy patients (TLE) and a matched control sample. We are aware that this sample was low power in terms of subjects and trials. However, collecting patients at the hospital is a difficult task that most of the time could take years. Although it would be interesting to extend the sample, previous studies with a lower number of patients (n=5) have demonstrated, behaviourally, the interrelationship of hippocampal dysfunction with memory integration and other cognitive functions (Pajkert et al., 2017). Regarding the number of trials, we ran several pilot patient's studies with a higher number of trials which resulted in difficulty for the patients. Therefore, extending the number of trials was deemed unfeasible. It would also have been interesting to have a separate sample of patients with PFC deficits, as the mPFC has previously been demonstrated to be crucial for the integration of information and a fundamental part of the connections between cortical and subcortical networks supporting episodic memories (Zeithamova, Dominick, & Preston, 2012).

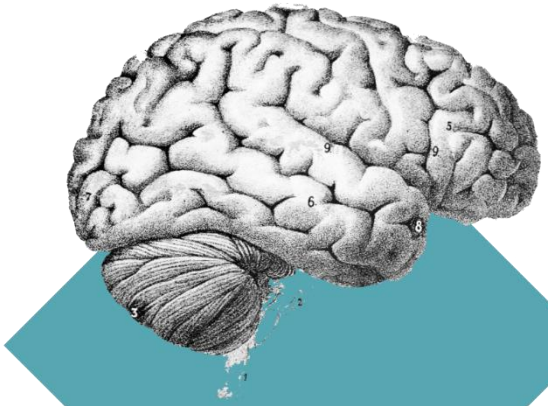
-In study 2 we wanted to investigate how collecting individual autobiographical stimuli could give us more insights into how recognition memory operates. Episodic memory is often discussed as a solitary construct. However, experimental traditions have examined episodic memory with different approaches (lab-based stimuli vs autobiographical stimuli) but rarely compare the two. Moreover, when real-life stimuli was used, there is a tendency to homogenize experiences in order to have more experimental control (e.g. all participants experiencing the same path in a route around the university (Cabeza et al., 2004)). Although we are aware that experimental control is needed to run experimental research, technologies are evolving so quickly and the need to sample individual data in multiple different fields is a reality that is on the horizon. With this premise in mind we set-up an exploratory experiment that allowed us to extract individual information from each participant which was ensured by the neurophysiological correlates of recognition memory. Although we are aware that these kinds of experiments are risky and could have many concerns

in the sense of control of the experimental conditions, we believe that this method is necessary and could be very useful with patients, or with subjects that have rare conditions such as the case of GB Aphantasia.

-Regarding the sample size in Experiment 1, clearly a sample of 14 participants in EEG experiments is a low number and more data could have helped in order to have stronger conclusions. However, each participant required at least 3 sessions of experiments. For future research, it would be interesting to set-up a team of people to be able to run several experiments at the same time.

-Regarding the crucial comparison between lab-based and autobiographical material (Experiment 2), one of the limitations was that we did not achieve enough number of trials in the lab-based experiments to specify a proper comparison and conclusion. Lab-based experiments were set-up at the end of autobiographical experiments to avoid the participant needed to come to the lab on several occasions (they came at least 4 times). In future research, it would be ideal to have more lab-based experiments spread over time to avoid tiredness and fatigue to get more results.

-In study 3, we showed a sample of a preliminary study in which we are currently working that is trying to validate the effectiveness of the design protocol showed in study 2. In this study we examine real-life autobiographical memories at the individual level. This study gives us the opportunity to explore clinical implementation and the brain areas that we could not observe with EEG methods used in study 2. One of the limitations of the study is that the sample is small, and we could not infer strong conclusions. However, this study provides us with a valuable avenue of assessing behavioural and brain functioning at the individual level to be transferred into clinical scenarios.



Chapter 8

Future Research Directions

Chapter 8: Future Research Directions

This thesis has explored a promising line of research that examined the neural mechanisms that subserve the retrieval of autobiographical memories in realistic scenarios. We used real-life stimuli as cues that engaged memory retrieval operations at the individual level. I believe this sets a milestone to develop further research that aims to investigate memory outside the lab, in real-life contexts.

Research in clinical contexts

The first study that used real-life pictures to study memory and that appeared in a peer-review journal was a behavioural experiment by Berry et al., 2007 on a 63-year-old patient with limbic encephalitis. This patient's bilateral hippocampal lesions, although relatively mild, resulted in difficulty in retrieving both recent and remote autobiographical events. The researchers sought to evaluate whether the patient's ability to recall details about her life experiences could be improved by having her wear a camera and periodically review the photographic record of any notable (i.e., non-routine) events. Of particular interest was whether wearable camera-based rehearsal could outperform a more traditional written diary-based approach. Despite several methodological shortcomings, this proof-of-concept case study provided support for the notion that the photographs captured by wearable cameras might be particularly efficacious as cues for triggering the recall of autobiographical event details and bolstering the long-term retention of these memories. When fMRI data was later collected from this same patient (Berry et al., 2009), greater activity was observed across a network of brain regions typically associated with autobiographical retrieval when the patient reported recognition of photographs of an event that she had previously rehearsed using the camera reviewing procedure relative to rcognition of camera photographs for an event that had been exclusively rehearsed using the written diary procedure.

Similar encouraging results were obtained in other research for case studies, including an amnesic patient with a large right-lateralized MTL lesion caused by herpes simplex viral encephalitis (Loveday & Conway, 2011), mild cognitive impairment (Browne et al., 2011), mild-to-moderate Alzheimer's disease (Woodberry et al., 2015). Furthermore, by virtue of enhancing patients' ability to remember events from their daily lives, the use of wearable cameras may potentially give additional quality-of-life benefits. For intance, rehearsal of events using wearable camera photographs resulted in diminished anxiety and stress, as well as increased confidence for a patient with mild cognitive impairment (Browne et al., 2011).

It is important to consider which qualities of the photographs captured by wearable cameras make them so effective at cueing episodic recall and strengthening the later accessibility of event details. One advantage of photographs over verbal diary entries is the fact that pictorial stimuli are known to be associated with a better memory when compared to verbal stimuli (Snodgrass, Volvovitz, & Walfish, 1972). Even if the people, objects, or landmarks depicted within a given photograph are insufficient to elicit recall of the specific episode, the high degree of perceptual correspondence between a first-person perspective photograph and the visuospatial context in which the event was encoded may facilitate recollection.

Long-term memory and temporal lobe epilepsy

Complaints of memory difficulties are common among patients with epilepsy, particularly with temporal lobe epilepsy (TLE) where memory-related brain structures are directly involved when patients suffer a seizure. However, the reason for these memory complaints is often unclear, and patients frequently perform normally on standard neuropsychological memory tests.

Numerous studies and reviews have delineated the clinical neuropsychology of TLE, particularly with respect to lateralization of seizures within the classic visual/verbal memory framework and in comparison of pre- and post-surgery outcomes (Kapur & Prevett, 2003). The material-specific model of memory relies on the idea that, in people who are right-handed, the left temporal lobe sustains verbal memories, while the right temporal lobe sustains non-verbal memories. However, over the years, neuropsychological and neuroimaging studies have progressively challenged this model. For instance, non-verbal deficits have been less consistently associated with the right TLE than verbal memory has been with the left TLE, and aberrant lateralization of activation patterns have been demonstrated during material-specific memory tasks in functional neuroimaging studies.

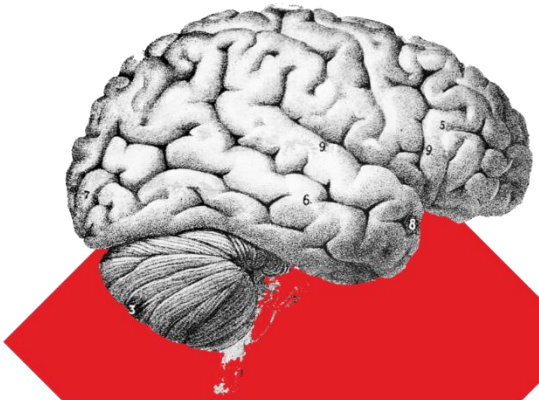
In recent years, additional issues challenging the traditional neuropsychological approach to TLE have emerged. Firstly, the severity of memory complaints has not been consistently captured by standardized neuropsychological assessment, with many TLE patients performing at average levels or above (Suresh et al., 2015). Standardized memory tests typically assess the ability to retain new information over relatively short (from 20 min to 1h) delays (Herman et al., 1997), whereas several lines of evidence suggest that TLE may also interfere with long-term consolidation, with successful memorized information after short delays progressively fading over periods of days or weeks. Secondly, paralleling the progress in our understanding of declarative memory organization, the possibility that TLE memory deficits might be analyzed beyond the scope of the verbal/visual dichotomy has been raised. One such approach is to

investigate the impact of TLE in autobiographical memories. This research has demonstrated that TLE patients show deficits in the ability to recollect personal episodic events from the past. More concretely, it has been demonstrated of a U-shaped autobiographical memory loss of periods encompassing most adult life, sparing however, the childhood, early adulthood and several recent weeks and the demonstration of a clear-cut dissociation between long-term consolidation of context-free material (single items and factual information) and context rich information (episodic memory)(Tramoni et al., 2011). Thus, this pattern of memory impairment leads to the conclusion that several aspects of memory functioning are altered in the long term and affect memory mechanisms that take place over long-term afecting daily life routine.

The current clinical project

We have recently launched a new project in collaboration with the epilepsy unit at the Hospital de Bellvitge that aimed to examine individual autobiographical memory in realistic scenarios in TLE patients with chronic epilepsy. To achieve this goal, we are sampling and recording real-life events from each of the individuals and controls in the daily life routine with the use of wearable cameras. One week after the data collection we scan patients and controls with fMRI methods while retrieving personal events through our validated autobiographical memory experimental protocol (see study 2 and study 3).

The group of patients included in the study are patients who are candidates for surgery. The results of this study could have great applications at observing which areas are important in the retrieval of autobiographical memories and must be preserved in order to avoid an impact on the autobiographical networks functioning that could affect their quality of life. We believe this is an example of a project that fosters basic to clinic knowledge transfer and that it may seemingly contribute to deepen understanding of how our brain is capable to transform the ongoing experience into an organized yet interrelated set of memory representations that can be accessible throughout our life span.



Chapter 9

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