

Space, Memory, Action: Insights from Behavior and Neurophysiology

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TESI DOCTORAL UPF / 2017

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Para Antón, Lucas y Cata

Acknowledgments

My deepest gratitude to my supervisor, Prof. Paul Verschure, for his support and guidance throughout all these years of thesis work. Doing research at SPECS has been an enlightening experience, and I am thankful for having the opportunity to work in such a challenging and active research group. My gratitude extends to all my colleagues. In particular, I thank Armin Duff and Marti Sánchez-Fibla, who contributed enormously to the design of the main experiments reported in the thesis. I am grateful to Riccardo Zucca and Diogo Pata, for their constructive feedback and insight in the intracranial studies. I thank Sytse Wierenga, for his critical suggestions and professional support, together with Pedro Omedas, in the Digital Heritage chapters of the dissertation.

Also, my sincere appreciation goes to Prof. Nikolai Axmacher from Ruhr University Bochum, who provided me with valuable guidance in the neurophysiology studies included in the thesis.

Finally, my most profound and strongest acknowledgment is for my family. I thank my parents, for their help and advice. I am grateful to my wife, Catalina, for her generous love and support during all these intense years. And especially, I thank my two boys, Lucas and Antón, for making the thesis period the happiest of my life.

Abstract

Human memory is fundamentally linked to experience. Traditionally, however, it has been studied in restricted tasks, under constrained experimental conditions. Understanding memory from a situated, embodied, spatial perspective constitutes not only a major scientific challenge but a primary issue in the design of future educational technologies. Indeed, recent developments in virtual and augmented reality (VR/AR) systems provide novel means to organize the interaction with digital content in fully spatial setups. A deeper insight into the behavioral determinants of memory is thus critical to build better Human-Computer Interaction (HCI) systems to visualize, explore and learn from data. In an interdisciplinary effort that integrates techniques from experimental psychology, HCI and neuroscience, this thesis presents a series of studies focused on the modulation of human long-term declarative memory by incidental and action-related factors. Our findings demonstrate the role of environmental information associated with items at encoding and retrieval on memory performance. In the brain, such spatial-context effect is observed in the early reinstatement of a combined spatial and stimulus-derived neural representation in the hippocampus during memory retrieval. Moreover, our data highlight the role of spatial context in shaping the underlying *structure* of long-term memory, which is observed in the strong statistical dependency of free recall recollection dynamics on the distance between items at encoding. Our results further underline the benefits of self-directed learning in mnemonic processing. We report enhan-

ced item recognition when timings and materials of study are volitionally determined by the learner as compared to passive memorization. Physiologically, active learning is characterized by increased theta oscillations in the hippocampus, in line with several studies which have linked this frequency band to active information sampling in the rodent. A key question arising from these findings is how to apply this knowledge in the design of new learning paradigms. Based on the principles of experience, embodiment, agency during the exploration of large corpus of data, we introduce an ecology of technologies aimed at the optimization of human-data interaction in the field of Digital Heritage. Altogether, our results advance our understanding of the behavioral determinants of human long-term declarative memory and their underlying physiological substrate, suggesting scientifically-grounded guidelines for the design of novel educational paradigms.

Resumen

La memoria humana está fundamentalmente ligada a la experiencia. Tradicionalmente, sin embargo, se ha estudiado en tareas restringidas, en condiciones experimentales limitadas. La comprensión de la memoria desde una perspectiva corporal, situada, espacial, constituye no sólo un desafío científico importante, sino una cuestión primordial en el diseño de las futuras tecnologías educativas. De hecho, mejoras recientes en sistemas de realidad virtual y aumentada (VR/AR) proporcionan nuevos medios para organizar la interacción con contenido digital en configuraciones completamente espaciales. Una visión más profunda de los determinantes conductuales de la memoria es, por lo tanto, crítica para construir mejores sistemas de interacción humano-ordenador (HCI) para la exploración y visualización de datos. En un esfuerzo interdisciplinario que integra técnicas de psicología experimental, HCI y neurociencia, esta tesis presenta una serie de estudios enfocados en la modulación de la memoria humana declarativa de largo plazo por factores incidentales y relacionados con la acción. Nuestros hallazgos demuestran el papel de la información ambiental asociada a elementos durante la codificación y la recuperación en el rendimiento de la memoria. En el cerebro, este efecto de contexto espacial se observa en la repetición temprana, durante el recuerdo, de una representación neuronal conjunta de contexto y estímulos en el hipocampo. Además, nuestros datos ponen de relieve el papel del contexto espacial en la configuración de la *estructura* de la memoria de largo plazo, lo que se observa en la fuerte dependencia estadís-

tica entre las dinámicas del recuerdo libre y la distancia entre los elementos durante la codificación. Nuestros resultados también subrayan los beneficios del aprendizaje autodirigido en el procesamiento mnemónico. Demostramos una mejor memoria de reconocimiento cuando los tiempos y materiales de estudio son determinados voluntariamente por el estudiante en comparación con la memorización pasiva. Fisiológicamente, el aprendizaje activo se caracteriza por un aumento de las oscilaciones theta en el hipocampo, en línea con varios estudios que han vinculado la banda al muestreo activo de información en el roedor. Una cuestión clave que surge de estos hallazgos es cómo aplicar este conocimiento en el diseño de nuevos paradigmas de aprendizaje. Basado en los principios de la experiencia, la corporalidad y la acción durante la exploración de datos, introducimos una ecología de tecnologías dirigidas a la optimización de la interacción hombre-datos en el campo del patrimonio digital. En conjunto, nuestros resultados avanzan nuestra comprensión de la memoria humana declarativa de largo plazo, sus determinantes conductuales y substrato fisiológico, sugiriendo guías fundamentadas científicamente para el diseño de nuevos paradigmas educativos.

Resumen

La memòria humana està fonamentalment relacionada amb l'experiència. Tradicionalment, però, s'ha estudiat en tasques restringides, sota condicions experimentals limitades. La comprensió de la memòria des d'una perspectiva espacial, corpòria i de presència constitueix no només un repte científic important, sinó una qüestió primordial en el disseny de futures tecnologies educatives. De fet, els desenvolupaments recents en sistemes de realitat virtual i augmentada (VR/AR) proporcionen nous mitjans per organitzar la interacció amb contingut digital en configuracions totalment espacials. Una visió més profunda dels determinants conductuals de la memòria és, per tant, fonamental per construir millors sistemes d'interacció humans-computadores (HCI) per visualitzar, explorar i aprendre de dades. En un esforç interdisciplinari que integra tècniques de psicologia experimental, HCI i neurociència, aquesta tesi presenta una sèrie d'estudis centrats en la modulació de la memòria humana declarativa a llarg termini, a través de factors incidentals i relacionats amb l'acció. Les nostres troballes demostren la influència del context ambiental associada a ítems en la codificació i recuperació en el rendiment de la memòria. Al cervell, aquest efecte de context espacial s'observa en la restauració primerenca, durant el record, d'una representació neuronal conjunta de context i estímuls en l'hipocamp. A més, les nostres dades ressalten la importància del paper que té el context espacial en la configuració de l'estructura de la memòria a llarg termini, que s'observa en la forta dependència estadística entre la dinàmica de recuperació lliure i la distància entre

ítems durant la codificació. Els nostres resultats també subratllen els beneficis de l'aprenentatge autodirigit en el processament mnemònic. Presentem un reconeixement millorat d'elements quan els temps i materials d'estudi són determinats voluntàriament per al estudiant en comparació amb una memorització passiva. Fisiològicament, l'aprenentatge actiu es caracteritza per l'augment de les oscil·lacions de theta en l'hipocamp, en línia amb diversos estudis que han vinculat aquesta banda de freqüències amb el mostreig d'informació activa en rosegadors. Una pregunta clau que sorgeix d'aquests resultats és com aplicar aquest coneixement en el disseny de nous paradigmes d'aprenentatge. Basant-nos en els principis d'experiència, realització i agència durant l'exploració de grans corpus de dades, introduïm una ecologia de tecnologies orientada a l'optimització de la interacció entre humans i dades en el camp del patrimoni digital. En conjunt, els nostres resultats avancen la nostra comprensió dels determinants conductuals de la memòria declarativa humana a llarg termini i el seu substrat fisiològic, suggerint pautes per al disseny de nous paradigmes educatius.

List of contributions

Contributions are listed in chronological order. Where applicable, the chapter of appearance is specified.

Contributions included in the thesis

Peer Reviewed

Pacheco, D. & Verschure, P.F.M.J. Long-term spatial clustering in free recall. *In press at Memory* [Chapter 4]

Pacheco, D., Sánchez-Fibla, M., Duff, A., & Verschure, P.F.M.J. (2017). A Spatial-Context Effect in Recognition Memory. *Frontiers in Behavioral Neuroscience*, 11. [Chapter 2].

Pacheco, D., Wierenga, S., Omedas, P., Wilbricht, S., Knoch, H., & Verschure, P.F.M.J. (2015), A Location-Based Augmented Reality System for the Spatial Interaction with Historical Datasets. *In Digital Heritage International Congress (DigitalHeritage), IEEE*. [Chapter 7]

Pacheco, D., Wierenga, S., Omedas, P., Wilbricht, S., Knoch, H., & Verschure, P.F.M.J. (2014, April). Spatializing experience: a framework for the geolocalization, visualization and exploration of historical data using VR/AR

technologies. In *Proceedings of the 2014 Virtual Reality International Conference* (p. 1). ACM. [Chapter 6]

Under Review / In preparation

Pacheco, D., Sánchez-Fibla, M., Principe, A., Rocamora, R., Zhang, H., Axmacher, N.*, & Verschure, P.F.M.J.* Coordinated representational reinstatement in hippocampus and lateral temporal cortex. * Contributed equally. *Manuscript in preparation*. [Chapter 3]

Pacheco, D., Sánchez-Fibla, M., Principe, A., Rocamora, R., Zhang, H., Axmacher, N. & Verschure, P.F.M.J. Theta waves in the human hippocampus during active learning. *Manuscript in preparation*. [Chapter 5]

Other contributions

Peer Reviewed

Pacheco, D., Zucca, R., Arsiwalla, X., Dalmazzo, D., Principe, A., Rocamora, R., Conesa, G. & Verschure, P.F.M.J. (2017). BrainX³ : a Virtual Reality tool for neurosurgical intervention in epilepsy. *Int J CARS (2017)* 12 (Suppl 1): S1–S286 S113. *Trans Bio-Med Eng*, 60, 1619-1627.

Verschure, P.F.M.J., Zucca, R., Pacheco, D., Santos-Pata, D., Maffei, G., Puigbó, J.Y., Arsiwalla, X.D., Principe, A., Conesa, G. & Rocamora, R. The neural code of the human brain as revealed by the analysis of intracranial recordings across a range of perceptual and cognitive tasks. *Society for Neuroscience 47th Annual Meeting, 2017*.

Pacheco, D., LeGroux, S. & Verschure P.F.M.J., Two Dimensional Shapes for Emotional Interfaces: Assessing the Influence of Angles, Curvature, Symmetry and Movement. *ACHI2015 : The Eighth International Conference on Advances in Computer-Human Interactions* (pp. 224-228).

Serra, L., Mura, A., Betella, A., Pacheco, D., Martinez, E., & Verschure, P.F.M.J., “Recovering the History of Bergen Belsen Using an Interactive 3D

Reconstruction in a Mixed Reality Space: The Role of Pre-knowledge on Memory Recollection.” In *Digital Heritage International Congress (Digital-Heritage)*, IEEE.

De Massari*, D., Pacheco*, D., Malekshahi, R., Betella, A., Verschure, P. F.M.J., Birbaumer, N., & Caria, A. (2014). Fast mental states decoding in mixed reality. *Frontiers in Behavioral Neuroscience*, 8, 415. * Contributed equally.

Betella, A., Pacheco, D., Zucca, R., Arsiwalla, X. D., Omedas, P., Lanata, A. et al., (2014). Interpreting psychophysiological states using unobtrusive wearable sensors in virtual reality. *ACHI2014: The Seventh International Conference on Advances in Computer-Human Interactions* (pp. 331-336).

Omedas, P., Betella, A., Zucca, R., Arsiwalla, X. D., Pacheco, D., Wagner, J., et al., XIM-Engine: a software framework to support the development of interactive applications that uses conscious and unconscious reactions in immersive mixed reality. In *Proceedings of the 2014 Virtual Reality International Conference* (pp. 30:1–30:2).

Romeo, M., Evans, A., Pacheco, D. & Blat, J. Domain Specific Sign Language Animation for Virtual Characters. *9th International Joint Conference on Computer Vision, Imaging and Computer Graphics Theory and Applications VISIGRAPP 2014*.

Evans, A., Agenjo, J., Abadia, J., Balaguer, M., Romeo, M., Pacheco, D., Ernesto Arroyo & Blat, J. Combining Educational MMO Games With Real Sporting Events. *6th Iberian Conference on Information Systems and Technologies (CISTI), 2011*.

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Introduction

This thesis studies the dependency of human long-term declarative memory on environmental context and active learning, employing behavioral and neurophysiological techniques. In this chapter, we present an historical overview of the scientific study of memory and describe its modern taxonomies. We review the current dominant theories of hippocampal function, given its critical role in long-term declarative memory. We introduce our research questions and methods, and describe how they are integrated within modern memory research.

1.1 Historical Background

Memory has attracted scientists and philosophers since the birth of ancient civilizations (Yates, 1969; Gorfein and Hoffman, 1987). The systematic, experimental study of human memory, however, started with the work of Herman Ebbinghaus at the end of the XIX century. In one of his most famous experiments, Ebbinghaus memorized entire passages of Lord Byron's *Don Juan*, and tested his knowledge of them only 22 years later. Given the long time elapsed between the moments of acquisition and recall, he found himself unable to recite the fragments — his memories for them were entirely lost. In previous work, Ebbinghaus had developed a sensitive measure to assess memory by counting the number of attempts that were necessary to

achieve “complete mastery” in remembering a list of nonsensical syllables. When memorizing the passages of *Don Juan* again, he noticed that the *learning rate* at which he could achieve full performance was much higher than the first time (Kahana, 2012). Was at least part of the information he acquired long ago still available in his brain? Modern science has provided an affirmative answer to this question. Studies have shown that the structural synaptic changes that take place during learning persist in the brain even if memories cannot be consciously retrieved, facilitating re-acquisition (Hübener and Bonhoeffer, 2010; Poo et al., 2016). More than 100 years ago, however, the conceptualization of the phenomena of *priming* — or in Ebbinghaus words, *savings* —, pointed to a fundamental difference between conscious and unconscious memory types (Squire and Dede, 2015).

Around the same time, another psychologist and philosopher, William James (1842-1910), established a second important distinction. James described *primary* memory as the mental process that makes us aware of the “right now”, and *secondary* memory as the knowledge of an event or fact of which in the meantime we have not been thinking (James, 1890). Although his dual scheme was solely based on introspection, it was hugely influential on experimental and theoretical work that followed, leading to the modern division between short and long-term memory types. Fundamental concepts about memory were established during this flourishing period of memory research.

It was Georg Elias Müller (1850–1934) who first introduced the idea that memories take time to *consolidate* (Müller and Pilzecker, 1900; Lechner et al., 1999; McGaugh, 2000). The introspectionist school of psychology lead by Wilhelm Wundt (1832-1920) is credited to have first differentiated memories that include contextual information of the moment of learning and those that imply only a vague sense of familiarity about the studied material (Kahana, 2012). The notion that memories have a physiological substrate is attributed to Richard Semon (1859-1918), who coined the term *memory engram* (Semon, 1921). Years before, Santiago Ramón y Cajal (1852-1934) maintained that learning is represented in the brain as increases in the num-

bers of connections between neurons, visible in structural changes at the dendrites (DeFelipe, 2006). Semon's theory went a step further, pointing to the storage of a wholistic pattern that registers a particular experience, and whose reactivation is necessary for recollection (Schacter et al., 1978; Josselyn et al., 2015). Semon did not elaborate on the physical instantiation of the engram, but his theory influenced the work of Canadian psychologist Donald Hebb, who proposed that neurons undergo enduring strengthening of some of their synapses through their co-activation with presynaptic cells (Hebb, 1949). In Hebb's theory, short and long-term memories are distinguishable. Short term memory implies transient electrical activation of neurons: "reverberating" activity which does not involve a structural change in the brain. Long-term memory, on the contrary, is only possible through the physical transformation of neurons at their synapse (Hebb, 1949). Hebb's theory was groundbreaking. It bridged the gap between psychology and biology, converting memory into a tangible, physical phenomenon. However, in his model, short and long-term memories were part of a unitary system, enabled by the same circuits. In the years that followed, the study of individuals with brain damage provided physiological evidence of their difference.

The case of patient Henry Molaison, known by his initials H.M. until his death in 2008, is one of the most prominent examples. H.M. was an epileptic patient whose medial temporal lobe structures were resected in a surgical operation in 1953 (Scoville and Milner, 1957). The surgery removed the anterior and medial portion of his hippocampus and substantial parts of the perirhinal, entorhinal cortex and amygdala bilaterally (Annese et al., 2014). The amnesic consequences of the operation were overwhelming: Molaison was affected by *retrograde amnesia*, experiencing a lack of memory for the three years leading up to the surgery, and undergo a profound *anterograde amnesia*, losing his ability to form new long-term declarative memories (Scoville and Milner, 1957). The catastrophic results of the operation were completely unexpected at the time. Before H.M., memory was thought to be a unitary, distributed process, with specific cortical areas involved in the encoding of different types of information. His case directly pointed

to a specialization of function of the structures that were removed in long-term declarative memory, leading to the development of modern taxonomies (Eichenbaum, 2013; Squire, 2009).

1.2 Memory Taxonomies

The anterograde amnesia experienced by H.M. affected all of his memories irrespective of their sensory modality (Corkin, 1984). Nonetheless, H.M. preserved a general knowledge about the world and his life, including some vivid childhood memories. He was not affected by any procedural impairment — he could develop new motor memories after the surgery —, and had no difficulty in maintaining a normal conversation. He had a regular performance in the digit-span task, a classic test that measures the number of items that a person can hold in memory without making errors (Corkin, 2013). The pattern of damaged and spared memories he experienced indicated that memory is not a unitary phenomenon, but there are multiple, dissociable types.

A primary distinction is between short and long-term memory. Short-term memory is the ability to hold in mind information, often through rehearsal, for a few seconds (typically 15~30s). It was initially believed to be a unitary process (Atkinson and Shiffrin, 1968), with a storage capacity of seven plus two “chunked” items (Miller, 1956). Further elaboration indicated a multi-component structure (Baddeley, 1992), whose storage limits can be better assessed by the quality or precision of the information encoded rather than the absolute number of items (Ma et al., 2014). The term working memory was coined to account for the different processes of *temporary storage* and *manipulation* of the information necessary for complex cognitive tasks (Baddeley, 2003). Three main components within working memory have been distinguished, including a control system — the “central executive” —, which is assisted by two auxiliary storage systems: the “phonological loop”, and the “visuospatial sketchpad” (all terms coined by Baddeley and Hitch, 1974; see also Baddeley, 2003). The exact limits of the short-term

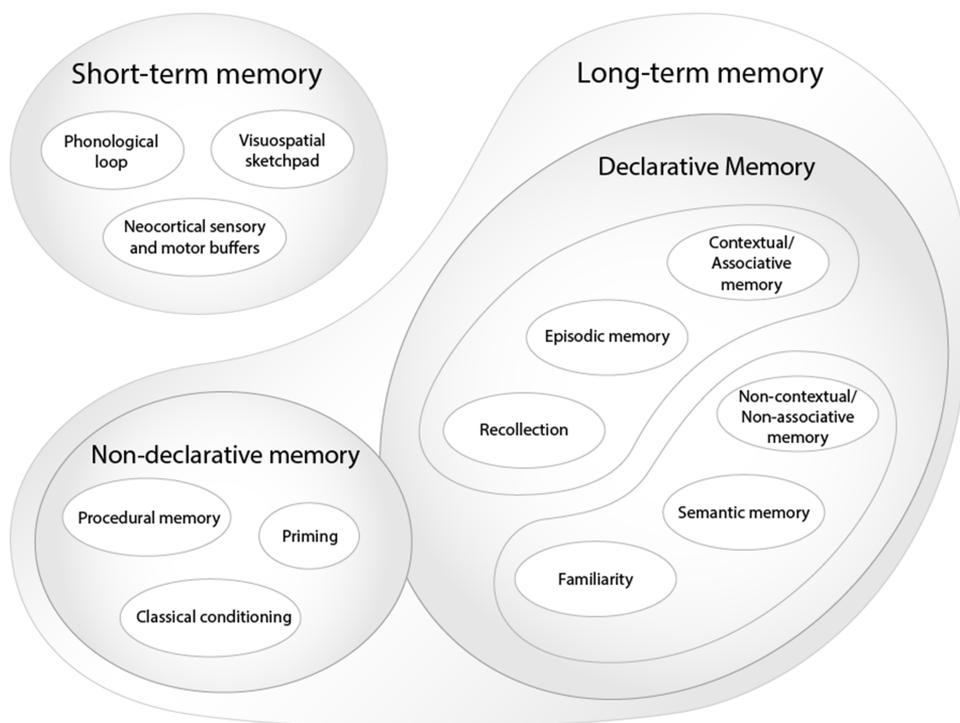


Figure 1.1: Taxonomies of memory (adapted from Bird and Burgess, 2008). Three major distinctions have been established between short and long-term memory, declarative and non-declarative, episodic and semantic.

span are diffuse. Theories have proposed that working memory exists to improve perception and prediction, and therefore the limits are defined by increases in prediction error e.g., during ill-fitted representations with respect to the current context (Zacks et al., 2007). In everyday life, working memory is often confused with *recent* long-term memory. In the experimental literature, studies typically assess long-term memory with tests that are conducted minutes after learning (Kahana, 2012). Long-term memory has a potentially unlimited capacity (Colgin et al., 2008; Buzsáki and Moser, 2013) and can last for a life span.

A second important differentiation is between memories that can be con-

sciously recollected and declared, and those that are implicit, inaccessible to consciousness (Squire and Dede, 2015; Schacter, 1992). Implicit or non-declarative memories include skills, habits, the phenomenon of priming, classical conditioning, and in general, all memories that can only be expressed through the *execution* of actions, i.e., procedural (Cohen et al., 1980). Priming refers to the facilitated identification of percepts or concepts from reduced cues as a consequence of prior exposure (Tulving et al., 1990; Schacter, 1992). For instance, if a person reads a list of words including the word *sunshine*, and is later required to complete a word starting with *sun*, the probability that he/she will answer *sunshine* is greater than if they are not primed. In classical conditioning, the acquisition of a conditioned response (e.g., an eye-blink) depends on the pairing of an initially neutral conditioned stimulus (e.g., a tone) with an aversive or appetitive unconditioned stimulus (e.g., an air-puff, Pavlov, 1927).

Declarative memories have been further divided into associative and non-associative. This distinction acknowledges the existence of memories which involve *recollection* of the specific contextual details of the moment of learning, and others that are based on a vague sense of *familiarity* of having previously encountered the material (Wixted, 2007). The recollection–familiarity distinction has been studied through the means of the *remember-know* paradigm (Wixted, 2009; Tulving, 1985), or, more in general, with recognition memory tests (Squire et al., 2007). In a traditional recognition experiment, the task is to discriminate between familiar items presented earlier during the learning session (targets) and new items not previously shown (lures). Two main views on recognition memory have been proposed. The dual-process theory holds that recollection and familiarity are two distinct memory processes, and that recollection is categorical (Yonelinas, 1994). Signal-detection theory, on the other hand, argues for a unitary mechanism in which recognition decisions are based on the *strength* of memory signal in relation to a decision criterion (Wixted, 2007).

A similar distinction is between *episodic* and *semantic* memories. Endel Tulving coined the term *episodic* to refer to a specific type of memory that

contains detailed information about the time and place where it was formed (Tulving, 1972). *Semantic* memories, on the other hand, constitute discrete, abstract knowledge, isolated from any contextual association (Collins and Quillian, 1969). Episodic memories are conscious memories which can be vividly re-experienced, as if implying “mental time travel” (Tulving, 2002). In animal studies, the term episodic-like memory has been preferred (Eacott et al., 2005). Autobiographical memories are typically episodic, but the term more generally refers to memories for personally experienced events. In cases of amnesia, when access to episodic memories is lost, memories of old events that survive tend to be semantic, i.e., stereotyped scripts rather than vivid narratives rich in contextual details (Steinvorth et al., 2005). A diagram with the traditional taxonomies of memory is presented in Figure 1.1.

Fundamental facts about memory have been established throughout the history of its scientific study. We have outlined the main conceptual distinctions regarding memory types and explained that different memory processes are subserved by different brain areas. At the beginning of this chapter, we stated this thesis would focus on the study of long-term declarative memory and its context-dependent nature. After the case of patient H.M., it became clear that this specific type of memory is critically dependent on the hippocampus.

But the hippocampus has been linked to a number of other cognitive functions in the neuroscience literature. Starting in the 70’s, for instance, a second important research tradition approached its study from the perspective of spatial navigation in the rat. Today, investigations have linked the hippocampus to the coordination of activity between brain regions in the service of self-directed learning (Voss et al., 2011a,b). Given the great importance of the hippocampus to the main questions of this dissertation (i.e., the modulation of human long-term memory by context and human action), a deep understanding of its role is required. Thus, in the following section, we review the most important theories of hippocampal function developed in the literature in the last fifty years.

1.3 Theories of hippocampal function

Two main narratives have dominated the debate on the role of the hippocampus in modern science. The first emphasizes a role in spatial processing, and is widely based on the study of the rodent neurophysiology. The second, developed after the case of patient H.M., has pointed to its specific role in human long-term episodic memory.

1.3.1 The spatial tradition

The “spatial” narrative started with the groundbreaking discovery of *place cells* in the hippocampus of rats (O’Keefe and Dostrovsky, 1971), i.e., neurons whose firing rate encodes the position of the animal from an allocentric perspective. After their discovery, place cells were considered the physiological substrate of a theoretical “Cognitive Map” predicted decades earlier by Tolman et al. (1948). The Cognitive Map Theory of hippocampal function (O’Keefe and Nadel, 1978) proposes a primary role of the hippocampus in the storage of allocentric representations of space to aid flexible navigation. In humans, these predominantly spatial processes evolved to support the spatiotemporal context of episodic memory (Bird and Burgess, 2008). According to the theory, the spatial map originally developed to subserve navigational purposes can be seen as a *scaffold* on which sensory information is both stored and organized (Nadel, 2008).

In modern versions of the theory, the primary function of the hippocampus is thought to be the construction of spatial scenes (Mullally et al., 2012; Maguire and Mullally, 2013). A role in mental scene construction would explain the involvement of the hippocampus in navigation, episodic remembering, and the imagination of future and fictitious events (Schacter and Addis, 2009; Hassabis et al., 2007; but see Dede et al., 2016b).

Although the Cognitive Map view originally proposed an exclusive role of the hippocampus in spatial processing, modern views have also acknowledged the importance of the Medial Entorhinal Cortex (MEC) in that function (Bird et al., 2012). Indeed, several types of spatially tuned cells have

been discovered in the MEC over the last decades, including Head Direction (Taube et al., 1990), Grid (Hafting et al., 2005), Border (Solstad et al., 2008) and Speed (Kropff et al., 2015) cells. MEC cells are largely unaffected by sensory cues from the environment, pointing to a specialized function in path integration from self-motion and internally generated signals (Derdikman and Moser, 2010; Moser et al., 2008). In the hippocampus, a joint representation of spatial inputs arriving from the MEC and sensory inputs coming from LEC is formed in the service of memory (Rennó-Costa et al., 2010).

1.3.2 The “mnemonic” view

A second important tradition emphasized a pivotal role of the hippocampus and Medial Temporal Lobe (MTL) structures in human autobiographical memory. This approach started with patient H.M. and the consequences of the removal of its hippocampus and adjacent structures. Probably the most influential theory in this tradition is **Declarative Theory** (DT), also known as the *standard model* (Squire and Zola-Morgan, 1991; Alvarez and Squire, 1994). Declarative theory argues that the hippocampus proper, the entorhinal, perirhinal, and parahippocampal cortices comprise an “MTL memory system” that collectively supports memory for facts and events (Squire and Zola-Morgan, 1991; Alvarez and Squire, 1994). The theory proposes that: 1) The hippocampus and adjacent regions are crucial for all forms of long-term declarative memory for a limited period, after which memories are consolidated in neocortical sites. 2) Consolidated memories, as well as short-term and implicit memories, are unaffected by medial temporal lobe damage (Squire and Zola-Morgan, 1991). 3) MTL supports memory for single items and associations broadly, with no specialized functional regions (Smith et al., 2011; Dede et al., 2016a). 4) MTL is specifically involved in conscious memories. Hence, DT proposes a unique function of MTL which is necessary for long-term declarative memory, and exclusively dedicated to it in a time-limited manner.

Most of the postulates of the standard model have been challenged (Nadel

and Hardt, 2011; Eichenbaum, 2013). First, alternative views on MTL function such as **Multiple-Trace Theory** (MTT, Moscovitch et al., 2005; Nadel and Moscovitch, 1997) have argued that episodic memories remain hippocampal dependent for a life span, and only semantic memories are unaffected by hippocampal damage. MTT proposes that the hippocampus registers an *index* of memories which is reactivated every time a memory is recalled, making retrieved memories less susceptible to disruption. Second, numerous studies have reported the engagement of the hippocampus and MTL in perceptual and short-term memory tasks (Peterson, 1994; Peterson and Gibson, 1994). Reports have further argued for a role of the hippocampus in coordinating attentional and control systems during information sampling in the service of learning (Voss et al., 2011a,b). This contradicts a main postulate of DT according to which short-term memories are unaffected by hippocampal damage. Third, experimental data has supported a role of the hippocampus in recollection but not familiarity based recognition, which is subserved by the perirhinal cortex (Davachi, 2006; Eichenbaum et al., 2007, 2012; Aggleton and Brown, 1999; Haskins et al., 2008). This view is in conflict with the idea of DT of an equal involvement of hippocampus in both processes which are distinguishable by their memory strength (Smith et al., 2011), or their content and *timings* (Staresina et al., 2012). Moreover, accounts have highlighted the critical role of the retrosplenial cortex on memory, an area not included in Declarative Theory (Ranganath and Ritchey, 2012). Finally, it has been shown that the MTL is involved in the encoding of unconscious memories (Henke, 2010; Ryan et al., 2000). This is problematic for the DT model given its argument of an exclusive dedication of MTL to declarative memory.

Despite these challenges, Declarative Theory has structured the debate on the neural circuits underlying long-term memory in the last decades.

1.3.3 Convergence, Relational Theory and derivatives

The spatial and mnemonic views of the hippocampus seemed unbridgeable for long time, but in recent years, several efforts have been made to reconcile

them (Moser et al., 2015; Burgess et al., 2002; Bird and Burgess, 2008; Morris, 2007).

An example is **Relational Theory** (RT, Eichenbaum, 1993, 2004), which argues that the main function of the hippocampus is to flexibly link information represented in cortical modules that could not otherwise communicate (Eichenbaum and Cohen, 2004). For RT, spatial processing is one example of relational processing, in which distinct multiple elements are integrated into a spatial scene (Cohen et al., 1997; Konkel and Cohen, 2009). Flexible relational associations are necessary for spatial and mnemonic processing but not restricted to them. Indeed, the RT points to a critical role of the hippocampus in inferential learning of non-spatial information in animals (Eichenbaum et al., 1999).

Several findings linking the hippocampus to the encoding of non-spatial, continuous variables have been considered “natural extensions” of RT (Eichenbaum, 2017; Eichenbaum and Cohen, 2014; Schiller et al., 2015). For instance, when rats run on treadmills, populations hippocampal cells encode the duration of the runs, irrespective of speed or distance travelled (MacDonald et al., 2011; Kraus et al., 2013). The mapping of time resembles that of space, with individual cells activating at specific delay periods throughout the run (“time fields”, Salz et al., 2016; Eichenbaum, 2014). A second line of evidence comes from studies showing hippocampal and MTL engagement in non-spatial navigation (Buzsáki and Moser, 2013). For instance, Aronov et al. (2017) trained rats to control the pitch of a sound with a joystick and reach specific audible frequencies. Hippocampal neurons developed “frequency fields” when animals translated within the sound space. The hippocampus has also been shown to map complex social space in humans, as assessed in a recent fMRI study (Tavares et al., 2015).

RT provides a framework that explains seemingly unrelated functions assigned to the hippocampus in the literature. However, important questions still remain. RT has criticized “limited-domain accounts” of hippocampal function, and the “specialness” hypothesis (Nadel, 2008), by which spatial

processing would have a privileged representation. Does the hippocampus indiscriminately represent all dimensions of experience? Is it biased to more strongly represent space and time? It has been argued that the hippocampus generates “context maps” — similar to the Cognitive Maps proposed by Tolman et al. (1948) —, and uses them to organize experience and guide behavior across all domains of cognition (Schiller et al., 2015; Ekstrom and Ranganath, 2017). Given the constraints of the physical world, however, the hippocampus has evolved to generate contextual maps in a 4D spatiotemporal framework, encoding permanently those variables. How flexibly it can switch to the representation of other continuous variables within that spatiotemporal framework remains to be determined in future research (Ekstrom and Ranganath, 2017).

We have reviewed the main theories of hippocampal function, highlighting its critical involvement in mnemonic and spatial processing. In the following section, we examine how the hippocampus is involved in the processing of contextual information, and how, at a physiological level, spatial and mnemonic signals interact.

1.4 The physiology of memory in the MTL

Throughout the vertebrates evolution, the anatomical and functional principles of organization of the MTL have been largely preserved. In this section, we review mechanisms of long-term memory formation, consolidation, and retrieval in the mammalian brain. We focus specifically on the role of individual neurons, circuits, and brain oscillations.

This section is particularly relevant for the two intracranial studies presented in this dissertation. Given the relevance of hippocampal processing of context for the experiment described in Chapter 3, we study how contextual information is represented in hippocampal neurons and brain oscillations. We first review single-unit studies in animals and humans and then focus on the role of frequency-specific brain rhythms. We highlight studies which have explored modulations in power and particularly in the theta (4-8Hz)

band with respect to memory and navigation, and link them to our results in Chapter 5. Finally, we review the literature on neural reinstatement, i.e., the replay of neural patterns present at the moment of learning during memory retrieval, and link it to our methods in Chapter 3.

1.4.1 Single-cell studies

Probably the most studied cells in the hippocampal-entorhinal system are *place cells* (O'Keefe and Dostrovsky, 1971), whose firing rate encodes allocentric space (Figure 1.2). Initially thought to subservise only spatial processing, their sensitivity to other types of sensory information such as odors, colors, objects was early acknowledged (Muller et al., 1991; Bunsey and Eichenbaum, 1996; Bostock et al., 1991; O'Keefe, 1976). Their modulation by behavioral context was subsequently reported, including modulations in firing patterns related to the current task or behavioral goal of the animal (Wood et al., 2000).

The observation that place cells encode changes in the environment by modulations of their firing rate was termed *remapping* (Muller and Kubie, 1987; Leutgeb et al., 2005). Two types of remapping were identified: *Global remapping* refers to changes in firing patterns that involve a shift in the location of place fields. *Rate remapping* points to changes in firing rate when place fields' locations are maintained. Remapping has been theorized to play a key role in mnemonic processing. First, it illustrates the joint coding of spatial and stimulus-derived information by the same neurons, facilitating the associations of elements with their context (Rennó-Costa et al., 2010). Second, it helps in the production of orthogonal, non-overlapping representations from similar inputs — a process known as *pattern separation* (Colgin et al., 2008). Pattern separation is a fundamental mechanism to distinguish memories that are similar. A related concept is *pattern completion*, a process by which a group of neurons restores a given pattern of activity (attractor) from partial input. The classical formulation of an attractor network is a Hopfield network (Hopfield, 1982), a type of network with a fixed-point attractor built from binary threshold nodes. Pattern sep-

aration and completion are two fundamental mnemonic processes that take place simultaneously in the hippocampus. In the Dentate Gyrus, the high number of cells compared to its main input, the Entorhinal Cortex, supports a role in pattern separation. In CA3 area, the strong local connectivity of neurons is ideally suited for pattern completion computations (Leutgeb and Leutgeb, 2007; Rolls, 2013; Rennó-Costa et al., 2014).

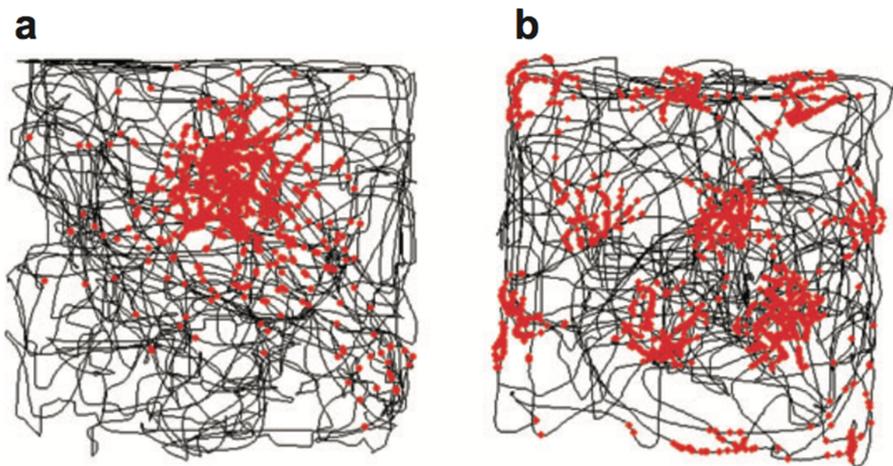


Figure 1.2: Place cell in the hippocampus (a) and grid cell in the MEC (b). The neuron’s spikes (red dots) are plotted on top of the animal’s trajectory (black line). Typically, place cells discharge in a unique spatial location, forming only one place field, whereas the firing patterns of grid cells form a periodic triangular matrix similar to a chinese checkboard. Extracted from (Moser et al., 2008).

In addition to place cells in the hippocampus, *grid cells* in the MEC underlie important navigation and (possibly) mnemonic processes (Figure 1.2). Grid cells are place-modulated neurons whose multiple “place fields” define a periodic triangular array covering the entire environment accessible by the animal (Hafting et al., 2005). They have been studied in bats and monkeys since their discovery in the Entorhinal Cortex (EC) of rats in 2005. In humans, the existence of grid-like activity in the EC was first shown in fMRI. Doeller et al. (2010) developed a technique to detect a macroscopic grid signal by contrasting brain activity during virtual movements aligned versus misaligned to the main axes of an hypothetical population of grid

cells. Subsequent research provided direct electrophysiological evidence of grid cells in the EC of neurosurgical patients (Jacobs et al., 2013).

Being driven by self-motion signals, grid cells were thought to provide the hippocampus with a universal metric for space (Fyhn et al., 2007; Moser et al., 2008). However, recent findings have shown that the grid is distorted in the borders and anchored to the salient landmarks of an environment (Rowland et al., 2016). The specific role of grid cells in memory is not well understood. Theoretical work has suggested a role in the MEC during hippocampal remapping, highlighting that to fit the experimental data in rodents grid cell inputs to Dentate Gyrus and CA3 should constitute around 30% of the total, while the remaining 70% corresponds to inputs from the Lateral Entorhinal Cortex (LEC, Rennó-Costa et al., 2010). This indicates a relevant role of action relation signals in the modulation of hippocampal dynamics and the formation of memories in CA3 and Dentate Gyrus neurons.

A correlation between grid-cell like representations in the right EC and Alzheimer’s disease has been recently shown. Kunz et al. (2015) reported reduced grid cell-like activity in carriers of the $\epsilon 4$ -allele of the APOE gene, one of the best predictors of late onset type (Corder et al., 1993). In a virtual navigation task, APOE $\epsilon 4$ -carriers had impaired spatial memory performance and compensatory hippocampal BOLD activations not observed in the age-matched controls.

In parallel to the characterization of place and grid cells and the study of their role in navigation and memory, studies have explored how individual MTL cells contribute to memory, independently of their responsiveness to spatial inputs. It was first demonstrated that neurons in the hippocampus, amygdala and entorhinal cortex are sensitive to specific object categories (Fried et al., 1997; Kreiman et al., 2000a). Interestingly, category cells show “identical selectivity” for visualizing a stimulus or imagining it (Kreiman et al., 2000b). The selectivity of individual neurons is not restricted to categorical representation but includes the coding of highly spe-

cific concepts. For instance, hippocampal CA1 cells selectively respond to individuals' identities, e.g., famous people, irrespective of the modality of presentation (Quiroga et al., 2005). A role of *concept cells* in long-term memory has been suggested based on four empirical findings: 1) their long-latency of firing, 2) their increased engagement in the encoding of personally relevant concepts, 3) their invariance with respect to the sensory modality of presentation, 4) their sparse and non-topographic representation (Quiroga, 2012).

Yet, studies have distinguished neurons in the MTL which are only “visually” selective (i.e., category selective), from those that respond to the novelty or familiarity of the presented material (Xiang and Brown, 1998; Viskontas et al., 2006; Rutishauser et al., 2006). Critically, it was found that only the latter correlate with participants confidence judgements (Rutishauser et al., 2015). The finding of “memory selective” neurons is consistent with theories of recognition memory which are based on the existence of a memory signal with variable *strength* (Wixted, 2007). The *strength* signal must be read at a population level given that memory selective neurons react only to their preferred category (i.e., either novelty or familiarity) with increases in firing rate (Rutishauser et al., 2015).

Further evidence of a specific role of MTL neurons in human memory has been provided by studies assessing their role in signaling specific items during learning and retrieval. It was first shown that hippocampal, amygdala and EC neurons that are active during encoding also activate before participants report their answers in the retrieval phase of a free-recall experiment (Cameron et al., 2001; Gelbard-Sagiv et al., 2008). More recently, context-specific reinstatement of locations was observed in a report investigating the phenomena of *spatial clustering*, by which items encountered at proximate locations during learning tend to be recalled consecutively in free-recall (Miller et al., 2013a). The study found that *place cells* that fire when items are encoded at specific locations during spatial exploration also discharge when participants report the items encoded at those locations and close by.

Electrophysiological evidence of reinstatement has also been observed in rodents (Tayler et al., 2013) and primates (Hoffman and McNaughton, 2002). More recently, a series of genetic tagging studies confirmed and extended previous electrophysiological findings in two ways: First, optogenetic studies have shown that when the reactivation of labeled neurons is compromised during retrieval, memories are disturbed (Berndt et al., 2016; Denny et al., 2014; Han et al., 2009; Hsiang et al., 2014; Park et al., 2016; Rashid et al., 2016). Second, the artificial reactivation of tagged cells induces the behavioral manifestation of specific memories (Cowansage et al., 2014; Liu et al., 2012; Ohkawa et al., 2015; Ramirez et al., 2013). Taken together, these results suggest that partial reinstatement of neural patterns is both necessary and sufficient for recalling particular memories (Richards and Frankland, 2017; Tonegawa et al., 2015).

Reinstatement might be accompanied by the *replay* of specific patterns across time and/or across neurons. The introduction of multi-unit recording techniques, in which the activity of hundreds of cells is captured in parallel, allows to assess distributed patterns of place cell activation during Sharp Wave Ripples (SWRs) episodes. SWRs are large amplitude negative polarity deflections (40–100 ms) associated with a fast 200Hz pattern in the hippocampal LFP (typically measured in CA1, Buzsáki, 1984, 2015). Studies conducted with rats found that the pattern of place cell activations during SWRs reflects previous trajectories experienced by the animals (Wilson et al., 1994; Lee and Wilson, 2002). Trajectories are not only replayed during sleep but also in the awake state of the rat, during immobility periods, in forward and reverse order (Foster and Wilson, 2006). Reports indicated that replayed trajectories are biased toward the animals' future paths (Pfeiffer and Foster, 2013; Singer et al., 2013). Yet replay also depicts *possible* trajectories in a given environment, not necessarily experienced or linked to the current position of the rat (Gupta et al., 2010). This led researchers to argue that pre-existing temporal sequences are mapped onto new experiences i.e., “preplay” (Dragoi and Tonegawa, 2011, 2013) — but see (Silva et al., 2015).

Replay has been shown to subserve the retrieval of specific memories (Wu et al., 2017), and its functional relevance during memory consolidation is well-established (Carr et al., 2011; Buzsáki, 2015). The idea that neuronal patterns which are formed during encoding are reinstated for consolidation was already proposed by Marr (1971). A modern version of Marr’s theory is the **Two-stage model** of memory consolidation advanced by Buzsáki (1984). The two stage model argues that the main role of SWRs is to replay patterns of activity to allow an efficient information transfer between the hippocampus and the neocortex (Buzsáki et al., 1994). Communication between the two regions is thought to be enabled by the nesting of SWRs, thalamic spindles and cortical low-frequency oscillations, a hierarchy of precisely timed oscillations (Staresina et al., 2015; Latchoumane et al., 2017). In accordance with the two stage model, simultaneous parallel replay has been observed in the hippocampus and the cortex during sleep in rats (Ji and Wilson, 2007). However, the notion of *transfer* has been challenged with the finding of prefrontal representations of fear memory at the very onset of learning (Kitamura et al., 2017).

Studies on neuronal reinstatement have revealed the particular contribution of single cells to mnemonic processing in animals and humans, indicating a critical role in both memory consolidation and retrieval. In addition to single-unit studies, research assessing the activity of large populations of neurons has revealed the reinstatement of item and context-specific neural representations in fMRI and intracranial EEG (iEEG, Zhang et al., 2017, see next section and Chapter 2).

1.4.2 Brain oscillations: LFP and Intracranial EEG studies

Since the early work of Hans Berger, who measured voltage changes in the brain through the means of a string galvanometer (Berger, 1929; Brazier, 1959), methods for recording extracellular electrical activity from neurons and neuronal ensembles have improved considerably (Buzsáki et al., 2012). Today, these include the electro-encephalogram (EEG) when voltage is recorded from the scalp and the electrocorticogram (ECoG) when sub-

dural strip or grid electrodes on the surface of the brain are used. When voltage is recorded with clinical depth electrodes (“macroelectrodes”, 1~1.5 mm in diameter) it is referred to as intracranial EEG (iEEG); when “micro-electrodes” ($\sim 40\mu\text{m}$ diameter) are employed, the term Local Field Potential (LFP) is preferred (Buzsáki et al., 2012; Mukamel and Fried, 2012; Johnson and Knight, 2015).

iEEG recordings present several advantages over non-invasive techniques. As highlighted in Mukamel and Fried (2012), these include: 1) Direct measurement of electrical activity, as opposed to functional magnetic resonance imaging (fMRI), or Positron-emission tomography (PET), which only capture the activity of neurons indirectly, 2) high spatial resolution (1~2 mm as compared to ~ 1 cm in MEG or scalp EEG), 3) high temporal resolution (milliseconds as compared to seconds in fMRI), 4) High signal to noise ratio (much less susceptible to artifacts as compared to scalp recordings). Limitations include typically the low number of subjects and their homogeneity when compared to studies with healthy participants, the sometimes limited coverage of implanted electrodes, and the fact that patients normally take medications for the treatment of their epilepsy which might affect their cognitive abilities.

Beyond these practical advantages and limitations, LFPs are a rich source of information (Buzsaki, 2006). Data decoded from oscillations reflects better behavior than that extracted from the firing rate of isolated neurons under some circumstances. For instance, the allocentric position of a rat in its environment can be better reconstructed from the hippocampal LFP when rats translate at high speeds as compared to Bayesian methods performed on single cells (Agarwal et al., 2014).

Traditionally, research on mnemonic processes with iEEG has focused on the study of Event Related Potentials (ERPs). ERPs are defined as the broadband electric brain response to a stimulus event averaged across trials (Luck, 2014). Despite their low frequency resolution and the limited insight they provide on the underlying neural processes, the literature on ERPs and

memory is vast (for reviews see Wagner et al., 1999; Rugg and Allan, 2000; Rugg and Curran, 2007).

Frequency-specific oscillations and memory

The role of frequency-specific oscillations has provided more specific insight into mnemonic processes. Traditionally, studies have explored the activity of five frequency bands, which have been associated with different cognitive processes: delta (1-4Hz), theta (4-8Hz), alpha (8-12Hz), beta (12-30Hz), and gamma (30-200Hz). In general, studies have linked theta and gamma rhythms in the hippocampus and MTL to learning and memory functions.

Theta has been widely studied in the animal literature. Specifically in the hippocampus, the rhythm has been linked to a long list of behaviors including voluntary movement and active information sampling (Vanderwolf, 1969; Buzsaki, 2006). Functionally, theta is considered the “on-line” state of the hippocampus (Buzsáki, 2002). Its most clear behavioral correlate in rodents is simply translation in space: when animals move, the hippocampal network is strongly dominated by the theta rhythm, while the specific frequency within the 4-8Hz range is modulated by speed (McFarland et al., 1974; Buzsaki, 2006; Colgin, 2016). In addition to its role in spatial navigation, studies have demonstrated a role of theta in different types of memory including associative learning (Berry and Thompson, 1978; Seager et al., 2002), and classical conditioning (Nokia et al., 2008; Miller, 2013).

Contrary to the animal literature, investigations assessing the specific role of theta oscillations in human memory have presented mixed results. Some studies have found that neocortical 4-8Hz oscillations play a role in long-term memory, working memory, and navigation (Tesche and Karhu, 2000; Stephen et al., 2005; Guderian et al., 2009; for a review, see Jacobs and Kahana, 2010). However, evidence for a specific role of hippocampal theta power in human memory is equivocal. While some investigations have reported increased oscillations in this frequency range during successful encoding (Lega et al., 2012; Fell et al., 2011), others have presented null results (Rutishauser et al., 2010).

It has been argued that the functional correlate of the rodent hippocampal theta is in the delta range in humans (Jacobs, 2014). When humans translate in VR, predominant oscillations are observed in the 1-4Hz band, which last for approximately 2.75 cycles (a shorter duration than the 4.3 cycles observed in the rat, Ekstrom et al., 2005; Watrous et al., 2011, 2013a). However, it is also possible that the lower frequencies observed in human studies are related to the use of stationary VR. Indeed, a recent experiment examined iEEG in patients that were allowed to move freely, revealing a consistent increase in the power of high-frequency theta oscillations (7-9Hz, Bohbot et al., 2017, see also Aghajani et al., 2016), in addition to low-frequency theta. The debate whether a functional equivalent of the rodent theta is present in other mammalian species is not settled. Studies have shown hippocampal low-frequency oscillations in cats, dogs and monkeys with similar functional roles than rodent theta but with different specific frequencies (Miller, 2013).

In this dissertation, we have explored the specific role of theta power in the hippocampus in Chapter 5. Our preliminary results suggest that low-theta oscillations play a role in active learning irrespective of performance in a subsequent recognition memory test.

Beyond modulations in power, a role of theta in synchronizing neuronal firing is well-established (Buzsáki, 2005; O'Keefe and Recce, 1993; Mizuseki et al., 2009). Several studies have reported hippocampal phase dependent long-term potentiation (LTP) in CA1, and a role of theta in orchestrating spike-timing-dependent plasticity (Buzsáki, 2005; O'Keefe and Recce, 1993; Huerta and Lisman, 1995). The relevance of theta synchrony is reflected in the increased recognition of items when MTL neurons discharge locked to the ongoing theta oscillation during learning, as has been shown in macaques (Jutras et al., 2009) and humans (Rutishauser et al., 2010). Synchrony of neurons in the prefrontal cortex and the hippocampal theta rhythm have also been reported in rodents (Siapas et al., 2005).

In addition to the coordinated firing of neurons with respect to the local LFP in the theta band, studies have reported a key function of theta gamma

phase-amplitude coupling (PAC) in mnemonic processes. It has been argued that the nesting of gamma in specific cycles of theta is a broad mechanism to encode information in the brain (Lisman and Idiart, 1995; Lisman and Jensen, 2013). Specifically in the hippocampal area CA1, theta plays a key role in “routing” gamma inputs from the CA3 region or the Entorhinal Cortex (Montgomery and Buzsáki, 2007), segregating incoming patterns into those reflecting memories to be encoded or retrieved (Hasselmo et al., 2002).

Finally, theta coherence across regions has been shown to play a key role in mnemonic retrieval. Synchrony in the theta range between EC and frontal and temporal areas underlies the retrieval of old autobiographical memories (Steinvorth et al., 2010). Watrous et al. (2013b) found that low-frequency coherence between MTL, prefrontal and parietal cortex is increased for correctly retrieved spatial and temporal information, with a 1-4Hz synchrony for spatial and a 7-10Hz coherence for temporal memory.

A second important frequency band related to learning and memory in humans is gamma. Increases in gamma power have been consistently linked to successful memory in free recall and recognition paradigms (Sederberg et al., 2007; Long et al., 2014; Burke et al., 2014). Interestingly, studies have also reported *reductions* of low gamma ($< 40\text{Hz}$) power underlying successful memory in protocols for word-list learning (Fell et al., 2001; Sederberg et al., 2006) and spatial memory (Zhang et al., 2015).

Gamma synchrony across brain regions has also been shown to reliably affect the formation of memory. In humans, the synchronization of hippocampal and entorhinal gamma oscillations predicts successful encoding (Fell et al., 2001) and retrieval (Staresina et al., 2012).

Oscillatory reinstatement and memory processes

As reviewed above, reinstatement of single-unit, item-specific activity has been observed in the human MTL during mnemonic processing (Gelbard-Sagiv et al., 2008; Miller et al., 2013b). Several studies have complemented these findings reporting the representation of specific items in the activity of

large populations of neurons in fMRI and iEEG protocols (Watrous et al., 2015; Zhang et al., 2017). Early fMRI studies reported decoding of categorical representations of pictures from patterns of BOLD activity (Haxby et al., 2001; Polyn et al., 2005; Staresina et al., 2012; Xue et al., 2010). fMRI studies focusing specifically on memory have found reinstatement of patterns in the hippocampus (Ritchey et al., 2012).

Similarity between neural representations at encoding and retrieval has also been observed in oscillatory iEEG patterns. For instance, Manning et al. (2011) constructed feature vectors of frequency-specific power from several ECoG electrodes by concatenating activity in the five traditional frequency bands at encoding and retrieval in a free recall paradigm. Vectors associated with specific items at retrieval were more similar to those observed when the same items were studied as compared to neighboring list items, with similarity decreasing reliably with positional distance. Using a similar methodology in a paired-associates setup, Yaffe et al. (2014) studied spatial patterns distributed across channels and found that successful retrieval occurs with reinstatement of a gradually changing neural signal present during encoding. Finally, Zhang et al. (2015) exposed patients to navigation sequences within a virtual house and asked them later to retrieve the trajectories by indicating which routes to take at specific intersection points. Whole brain patterns of brain activity around 80Hz were more similar when participants recalled the same trajectories as opposed of different. The effect was enhanced for correctly retrieved sequences, indicating a critical role of oscillatory reinstatement in the quality of memory for events.

Several other studies have shown reinstatement of spatially distributed, frequency specific patterns of oscillatory power across time during the encoding and retrieval phases of a memory experiment (Ekstrom et al., 2007; Rey et al., 2014; van Gerven et al., 2013; Kraskov et al., 2007).

The finding of a “global engram“ captured by several sources across the brain has been complemented by a recent study showing higher local reinstatement of broadband oscillatory power in the anterior hippocampus during source

as compared to item recognition (Staresina et al., 2016). Source recognition implies ability to recognize an item together with its context of encoding, whereas item recognition refers to the recognition of the item without its context. In accordance with rodent studies reporting reinstatement of activity from highly localized cell assemblies (Liu et al., 2012; Tayler et al., 2013), the study of Staresina et al. (2016) capitalizes on the fact that firing patterns of distributed neurons in the hippocampus influence the LFP differentially. A unique pattern of activity deployed over time can be thus formed by the proportional contribution of multiple neuronal sources and captured by a single electrode.

In Chapter 3, we have used a similar method to study how the hippocampus and the Lateral Temporal Cortex (LTC) contribute to the formation of episodic memories. By assessing reinstatement of oscillatory power over time in these two regions simultaneously, we could observe a double dissociation between the reinstatement of items and their context (Chapter 3).

Neurophysiological studies have advanced our understanding of memory processes enormously. However, to develop better learning systems and improve educational practices, we also need to understand memory at a behavioral level. In the next section, we review the main behavioral determinants of memory identified in experimental psychology.

1.5 Behavioral determinants of memory in humans

1.5.1 Memory is context-dependent

According to the method of Loci, developed by the Greeks to remember lists, memory can be boosted if items to be remembered are arranged and integrated along a well known spatial route. Following the method, one has to form a visual image of each item to be recalled, and mentally locate that image at specific locations along the path. The image has to be integrated in the context where it is positioned i.e., relationships between features of the

environment and those of the items should be created, and at the moment of retrieval, the route has to be taken again mentally to find the items where they were first located.

The method has been continuously used over centuries with small modifications, and its wide use today in so called “memory olympics” (Foer, 2011; Maguire et al., 2003). In such competitions, the frontiers of human memory are established, and the best athletes can memorize hundreds of words, digits and randomly shuffled cards (Foer, 2011).

Why does the method work? It has been argued that its effectiveness relies in the creation of mental associations between known cues and previously unknown list items at input, and the use of these cues to guide recall (Bower, 1970). Indeed, the method emphasizes the associative nature of human memory, and the fact that memory can be *structured*.

In the same way that items can be mentally organized in imagined spaces, real, physical environments where learning and recalling take place strongly modulate human memory. Although early studies in experimental psychology questioned the relevance of environmental features (e.g., Godden and Baddeley, 1980; Smith et al., 1978; Fernandez and Glenberg, 1985), the role of spatial and contextual factors in memory for items is today well-established (Smith and Vela, 2001).

Several theoretical frameworks have been proposed to account for the context effects (particularly the spatial-context effects) observed in the literature. For instance, the Context Maintenance and Retrieval model (Polyn et al., 2009), which is an extension of the Temporal Context Model (Howard and Kahana, 2002), proposes that non-temporal factors such as semantic or spatial proximity affect free recall. In the model, context is seen as a gradually changing representation which includes external and internal information that cues memory search during free recall.

It has been argued that this continuously shifting context representation is modified more abruptly at the encounter of spatial frontiers (Horner et al., 2016). Studies have shown the role of spatial boundaries in weakening the

long-term links between information preceding and following them, organizing memory into discrete episodes (Ezzyat and Davachi, 2011; Zacks et al., 2007). This episodic organization creates statistical dependencies of elements composing events, such as items encoded together tend to be recalled in an all-or-none fashion (Horner and Burgess, 2014).

Beyond its role in contextualizing memory, space can be used as an organizer of items because of its relational, “configural” nature (Nadel, 2008). Indeed, it has been argued that mnemonics such as the method of Loci might work because of the association between items and a known framework. The linking of elements with a pre-existing cognitive map formed by place cells could capitalize on the connections between these cells to facilitate memory search (Lisman, 2015). In that sense space can be seen as a mental *schema* (Tse et al., 2007) on which unrelated information can be integrated, facilitating acquisition.

In this thesis, we have explored the context-dependent nature of human memory across several experiments. We have studied contextual effects on recognition memory from the perspectives of behavior (Chapter 2) and neurophysiology (Chapter 3). We have further investigated the role of spatial context on the structure of memory in Chapter 4. We provide an overview of our results in Chapter 8.

1.5.2 Memory depends on action

A second important factor that modulates human memory is agency, or the voluntary control over the learning process. Indeed, the distinction between active and passive learning has been a highly influential topic of investigation across different research fields. In educational sciences, it has been argued that people learn better when the materials and timings of study are under their control (i.e., learning is self-directed, Council et al., 1999; Sylva et al., 1976; Montessori, 2013). Several theories have argued for a critical role of the active engagement of the learner in studying the material. Instruction methods such as discovery learning (Bruner, 1961), experiential learning

(Kolb, 1984), and inquiry learning (Papert, 1980) all advocate situations in which students engage in active hypothesis testing, interaction with learning materials, and self-directed exploration.

In the scientific literature, not many experiments have explored the benefits of active learning. Empirical studies of human learning and memory are typically passive. Nevertheless, in general, the available evidence supports the notion that controlling the flow of information intake during learning enhances subsequent performance in memory tests (for a review, see Gureckis and Markant, 2012).

For instance, Kornell and Metcalfe (2006) compared performance in a semantic memory task when participants could decide on the materials to study versus that of a passive learning condition in which materials were assigned by the experimenters. The study found that subjects who choose which items to study performed better in the final test.

Across three experiments, Voss et al. (2011a) demonstrated the mnemonic benefits of cognitive agency in a task that consisted in remembering visual items and their positions in a two-dimensional array. In a first experiment, Voss et al. (2011a) compared performance in the task between volitional and passive learning conditions, i.e., between one with self-directed, continuous control of the elements and timings of study during learning, and a second in which subjects were passively exposed to the trajectory of another participant. The self-directed learning condition was associated with increased recognition of items and better spatial memory in a subsequent memory test. In a second experiment, subjects in the active condition could control navigation in 2D space but were guided on what items to explore with indications shown on the screen (“active deterministic”). In a third experiment, the passive condition was as in experiment 1, but participants were asked to mimic the movements seen on screen with the joystick (“manual passive”) condition. Participants in the “active deterministic” and “manual passive” learning conditions did not show memory improvements but performed as in the normal passive condition. Taken together, results from Voss et al.

(2011a) suggest that the increases observed in the recognition and spatial memory tests were related to the control of the flow of learning, i.e., the continuous decision of what items to study, in what order, and for how long.

Critically, the study of Voss et al. (2011a) reports higher engagement of the hippocampus in active conditions across experiments, as assessed by fMRI scans in a group of healthy subjects. Moreover, benefits of active learning were not observed in patients with hippocampal damage. This led us to explore, in Chapter 5, the electrophysiology of active learning, to complement and extend these brain imaging studies with a detailed time-frequency characterization of the process in the hippocampus.

Insights on the role of action in learning also come from the study of human behavior in the spatial navigation literature. Studies have explored the influence of active body movement in the understanding of space, and specifically, the strongest effect of podokinetic information (proprioceptive + vestibular) compared to other components of navigation in spatial learning. In general, results suggest that spatial learning is boosted in active (physical) versus passive navigation conditions (Chrastil and Warren, 2012; Taube et al., 2013; Chrastil, 2013; Grant and Magee, 1998; Ruddle et al., 2011b,a).

Throughout this dissertation, we have explored the benefits of cognitive agency during learning. We have investigated different forms of agency in Chapters 4 and 5. In Chapter 4, experiment two, subjects navigated a virtual environment and decided on the routes to take during navigation. In chapter 5, experiment one, participants in the active condition controlled not only their trajectory in space, but also what items they wanted to study, revisit, and the specific exposure times. Different results were obtained in the subsequent memory tests, and we further discuss them in Chapter 8.

1.5.3 Thesis outline

In the following chapters, we present a series of experiments in which we studied the role of context and human agency in the modulation of long-term declarative memory both at a behavioral and neurophysiological level.

We first examine the modulation of recognition memory by spatial-context in a VR-based navigation paradigm conducted with healthy human subjects. We show a consistent effect of the congruency of spatial information associated with items at learning and testing on memory performance (Chapter 2).

By running the same paradigm with epilepsy patients implanted with intracortical electrodes, we subsequently explore the neural signatures of the observed effect in the brain (Chapter 3). Our analyses reveal a coordinated reinstatement of item and context-specific patterns of activity in the hippocampus and lateral temporal cortex during memory retrieval.

In Chapter 4, we study the influence of space on the organization of items in long-term memory. We analyzed recollection dynamics in free recall of items learned during virtual navigation. We observed a statistical dependency of the order of recall and the Euclidian distance between items at encoding. We also found a correlation of spatial clustering scores and recollection performance, both in immediate and 24 hours delayed tests.

In Chapter 5, we explore the question of how memory is modulated by action. Previous fMRI studies have reported a greater activation of the hippocampus during self-directed as compared to passive memorization. We show that hippocampal engagement is characterized by higher theta power during active as opposed to passive information seeking.

In Chapter 6 and 7, we present a framework of technologies for the embodied interaction with historical data in outdoor settings in which ideas on the role of spatial-context and action on memory are tested and implemented.

A spatial-context effect in recognition memory

In this chapter, we study how memory is modulated by spatial context. In particular, we evaluate how the quality of recognition memory is affected when encoding and retrieval happen in the same, or in different environments. Our results show that recognition accuracy increases in trials in which the environments of learning and testing are the same as compared to those in which they are different. In the Discussion (section 2.4), we highlight the relevance of investigating the neural signatures of the observed effect in the brain, a problem we address in Chapter 3. The text presented here reproduces a publication entitled “A spatial-context effect in recognition memory”, published this year in the journal *Frontiers in Behavioral Neuroscience* (Pacheco et al., 2017). The abstract reads:

We designed a novel experiment to investigate the modulation of human recognition memory by environmental context. Participants were asked to navigate through a four-arm Virtual Reality (VR) maze in order to find and memorize discrete items presented at specific locations in the environment. They were later

on tested on their ability to recognize items as previously presented or new. By manipulating the spatial position of half of the studied items during the testing phase of our experiment, we could assess differences in performance related to the congruency of environmental information at encoding and retrieval. Our results revealed that spatial context had a significant effect on the quality of memory. In particular, we found that recognition performance was significantly better in trials in which contextual information was congruent as opposed to those in which it was different. Our results are in line with previous studies that have reported spatial-context effects in recognition memory, further characterizing their magnitude under ecologically valid experimental conditions.

2.1 Introduction

Traditionally, the study of the dependence of human memory on environmental context has been conducted under highly constrained laboratory conditions. In general, investigations have assessed the role of context by manipulating the congruency of discrete information associated to items during learning and testing. This has typically been achieved through the use of synthetic cues of specific sensory modalities in isolation, such as colors and position of items on the screen (Murnane and Phelps, 1994; Hockley, 2008), or auditory stimuli (Geiselman and Glenny, 1977; Geiselman and Bjork, 1980). Studies with a broader definition of context have explored the role of space in recognition memory, by assessing how the congruency of the environments of encoding and retrieval affects performance in recognition tests. In such paradigms, subjects are typically presented with items to be learned in one environment, and later on tested on their ability to recognize items in the same or a different environment. Under those circumstances, consistent spatial-context effects in recognition memory have been reported in the last decades (for a review and meta analysis, Smith and Vela, 2001).

However, key aspects of space that are known to affect memory in the animal literature have not been considered sufficiently in the environmental-context dependent memory field. In particular, theoretical work on the phenomenon of rate remapping has argued for a facilitation of memory retrieval when items are spatialized (Leutgeb et al., 2007; Rennó-Costa et al., 2010). Indeed, the retrieval of items associated with specific locations in space could benefit from pre-existing connections between hippocampal place cells depicting spatial trajectories (Lisman, 2015; Silva et al., 2015). Yet in traditional environmental-context dependent memory experiments, items have not been deployed spatially, but rather presented in a compressed form. Even in setups where environments of learning and testing are changed, stimuli are typically presented in a unique spatial location (i.e., a list of words to be read in or visual stimuli presented on a computer screen).

On the other hand, it has been shown that spatial memory in the mammalian brain is highly dependent on movement and action, being driven by a path integration signal (Rennó-Costa et al., 2010; Giocomo et al., 2011; Lu et al., 2013). Indeed, spatial information encoded by hippocampal place cells is significantly reduced when movement is restricted (Song et al., 2005; Chen et al., 2013). Yet, in previous investigations on context-dependent memory, participant's movements during encoding and retrieval has been constrained or uncontrolled (Smith and Vela, 2001). This contrast with the long tradition of experiments in the human navigation literature where the modulation of spatial learning by spatial behavior has been explored (Chrastil, 2013). While several of these studies have been conducted in outdoor setups, others have employed Desktop Virtual Reality (VR; Wilson et al., 1997; Christou and Bühlhoff, 1999; Gaunet et al., 2001; Carassa et al., 2002; for a review, see Chrastil and Warren, 2012). Although stationary VR does not assess the contribution of proprioceptive or vestibular information, it has a number of advantages that make it a valid tool for the study of human navigation. First, it captures information related to volition and cognitive decision making on the routes to take during way finding (Chrastil and Warren, 2012). Second, it has been shown to activate navigational sys-

tems of the brain including Place Cells in the hippocampus (Ekstrom et al., 2003), and Grid Cells in the Medial Entorhinal Cortex (MEC; Jacobs et al., 2013). Third, stationary VR allows the flexible manipulation of independent variables related to the configuration of space that would be otherwise impossible to handle (Tarr and Warren, 2002).

Grounded in the animal literature and previous theoretical work (Rennó-Costa et al., 2010), we aimed to test spatial-context effects in recognition memory under ecologically valid experimental conditions. We created a novel setup in which we associated discrete items to unique locations in a virtual maze. Following a within-groups methodology, we required the participants of our experiment to navigate the maze in order to find and memorize discrete images. We later on tested their ability to identify, from a new set of items, those previously presented from those that were new. Critically, we changed the contextual information associated with part of the old items during the retrieval phase of our experiment, in order to evaluate recognition memory for stimuli in congruent and incongruent spatial-context conditions.

Given the spatial context effects in recognition memory previously discussed, and the fact that we generated the conditions that are known to modulate memory in the hippocampus and the MEC, we predicted to observe a spatial context effect in our VR-based, spatial recognition test. In particular, we hypothesized to find better recognition performance and shorter decision times for items encoded in the congruent spatial context condition as compared to the incongruent one.

2.2 Materials and Methods

2.2.1 Participants

Participants were 33 young adults (20 male, mean age 23.78 ± 3.91 years) recruited from Universitat Pompeu Fabra’s (Barcelona, Spain) student community. All participants were explained about the procedures by the ex-

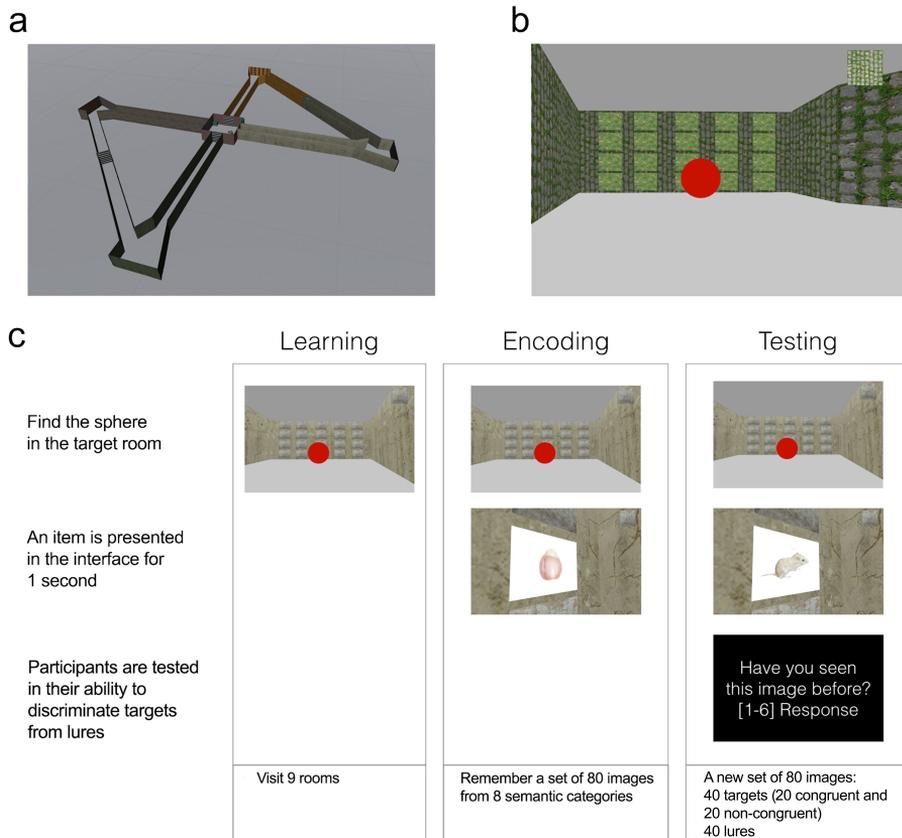


Figure 2.1: Task description. (A) A view showing the spatial layout of the maze. Four satellite rooms are connected to a central one. (B) Twenty items are positioned in one of the walls in each room forming a 5 × 4 matrix. The target room at each trial is indicated in the top right of the user interface (UI) with a texture. (C) Schematic showing a trial in each of the phases of the experiment.

perimenter and provided informed consent to participate in the study. The protocol was approved by the local Ethical Committee “Clinical Research Ethical Committee (CEIC) Parc de Salut Mar” (Barcelona, Spain).

2.2.2 Procedure

The experiment was organized in three main blocks: learning, encoding and retrieval. In all blocks, participants were asked to navigate a virtual maze

comprising a central and four satellite rooms (Figure 2.1 A). Each room had a unique visual texture on its walls (i.e., concrete, stone, brick and wood) and was connected to a second room and to the center room. During all blocks participants had to perform a navigation task, which consisted of finding a target room (indicated in the user interface, UI, Figure 2.1 B) and memorize (encoding block) or recognize (testing block) a discrete stimulus. A trial was defined as the action of reaching the room and memorize/recognize the correspondent stimulus. The starting position for the first trial in each block was set to the central room for all participants. The sequence of rooms to visit was randomized. In all blocks participants were instructed to perform the task until they visited all images. Participants experienced the 3D world sitting in front of a 32 computer screen and interacted with the application using the keyboard and the mouse. The VR application was created using the Unity3D game engine (Unity Technologies, San Francisco, CA, USA).

The experiment evolved over three blocks (Figure 2.1 C).

Learning block. The objective of the learning block was for the user to gain spatial knowledge of the maze before the start of memory encoding and to help participants to familiarize themselves with the interface. Before starting navigation, subjects were shown a map of the environment and explained the characteristics of the maze. During navigation, they were asked to reach the target room indicated in the UI at each trial, until they completed 10 rooms.

Encoding block. In the encoding block, subjects had to memorize 80 images that were encountered during navigation. Images were located in one of the walls of each room in a 5 × 4 matrix (20 images per room). The matrix was designed so that each item would be associated with a unique spatial context in the environment, determined by its location in the maze (room) and its position on the wall. When the target room was reached at each trial, the correspondent stimulus was presented for 1 s, and then made invisible for the rest of the block.

Testing block. In the testing block subjects were asked to navigate again and

visit a new set of 80 images (20 per room), from which half have been seen previously and half were new. As in the encoding phase, after reaching the target room at each trial, an item was revealed for 1 s. After stimulus presentation, subjects were asked to indicate whether they had seen the image in the previous block of the experiment using a 6 points confidence scale—from 1 (Sure unfamiliar) to 6 (Sure familiar) as in a traditional recognition memory experiment (Squire et al., 2007). The confidence question was presented in the UI and remained visible until participants reported their answers.

Two categories of items were distinguished: those presented in the same room and position on the wall matrix during the encoding and retrieval phases of the experiment (congruent items), and those presented in a different room and position on the wall (incongruent items).

All items (targets and lures) were extracted from the same pool of images belonging a dataset available in Moreno-Martínez and Montoro (2012). From the 360 objects in the dataset, a smaller pool of 160 items was selected from eight semantic categories (food, furniture, human body, musical instruments, buildings, tools, clothes and animals). For each subject separately, a subset of 80 images was selected randomly from this pool of 160 images, and assigned (again randomly) to specific conditions. In total, 20 images were assigned to the congruent condition and 20 to the incongruent condition. Eighty images were assigned to the “new” condition, from which 40 were presented during encoding and not shown at retrieval, and 40 were presented at retrieval but not shown during the encoding phase of the experiment.

Participants were not instructed to optimize their spatial behavior in order to find the shortest path connecting two rooms, but were informed about the spatial layout of the environment during the learning phase.

2.2.3 Dependent Variables

Three dependent variables were measured in the experiment.

Recognition accuracy: number of correct answers divided by the total number of trials in a correspondent condition.

Decision Time (DT): time elapsed from question onset until participant’s responses. We only considered correct responses and excluded trials in which it was more than 2.5 SD away from the mean for each participant separately.

Navigation Optimality: ratio between the shortest possible trajectory length connecting initial and target rooms at each trial and the actual trajectory length of that trial. The measurement ranges from 0 (if a subject never reaches the target room) to 1 (shortest trajectory length). Given the shape of the environment, only one possible combination of corridors connecting two rooms was the correct choice to achieve optimal performance. This measure was created to evaluate how well participants learnt the maze before the testing phase of the experiment.

A repeated measures ANOVA model was built to characterize the relationship between familiarity (novel/familiar), and confidence (high/low) with recognition performance. A second ANOVA model was constructed to quantify the influence of elapsed time (short/long) and old item condition (congruent – incongruent) on recognition performance. For the analysis of DTs we used a one-way ANOVA with factor item condition (old congruent – old incongruent – new). Pairwise *post hoc* comparisons were performed using paired t-tests. All reported *post hoc* tests are corrected for multiple comparisons using the Bonferroni method.

2.3 Results

2.3.1 Overall Results

We first aimed to evaluate if our VR based recognition test could capture the dynamics of recognition memory previously identified in traditional laboratory setups (Squire et al., 2007; Wixted, 2007). We conducted a Receiver Operating Characteristic (ROC) analysis for each participant, to assess how well they could discriminate targets and lures at different levels of confidence.

A ROC is simply a plot of the hit rate (old items are correctly identified as old) as a function of the false-alarm rate (new items are incorrectly identified as old) at different levels of confidence (Squire et al., 2007).

All participants performed above chance levels (0.5 for Hits and False Alarms, along the diagonal in Figures 2.2 A,B) at different levels of confidence. The average area under the curve (AUC) was 0.86 ± 0.01 (SE, Figure 2.2 B). As expected for declarative memories (Kahana, 2012), the z-ROC curve was asymmetrical along the chance diagonal (mean z-ROC slope = 0.86), indicating a greater variance in the distribution of the old items memory strength (Squire et al., 2007).

Participants responded in general with high confidence (74.9% of the trials, SE = 4.6%); medium and low confidence were assigned less frequently and in similar proportions (M = 17.4%, SE = 2.3% and M = 13.3%, SE = 1.7% respectively, Figure 2.2 C). Due to this unequal distribution, we pooled data from trials with intermediate and low confidence ratings for a comparison between high and low confidence with an equivalent number of samples. Normalized accuracy was significantly better in the high confidence group (0.89 ± 0.01 vs. 0.64 ± 0.02 ; main effect of confidence, $F_{(1,32)} = 97.9$, $p < 0.01$, $\eta^2 = 0.76$). *Post hoc* tests revealed that indeed performance for items retrieved with high confidence was significantly higher than low confidence trials $t_{(32)} = 9.98$, $p < 0.01$, $d = 1.73$, Figure 2.2 D.

In general, these results are consistent with a recent report that measured performance, confidence and decision times (DTs) in a traditional recognition memory experiment (Rutishauser et al., 2015), suggesting that the main features of recognition memory were well captured by our spatial test.

2.3.2 Spatial Behavior

The analysis of spatial behavior revealed that all four satellite rooms were occupied an equivalent amount of time across participants (Wood: M: 12.72 min, SD = 1.41 min, Stone: M = 12.9 min, SD = 1.57 min, Brick: M = 12.64 min, SD = 1.46 min, Concrete: M = 12.54 min, SD = 1.4 min, $F_{(3,96)}$

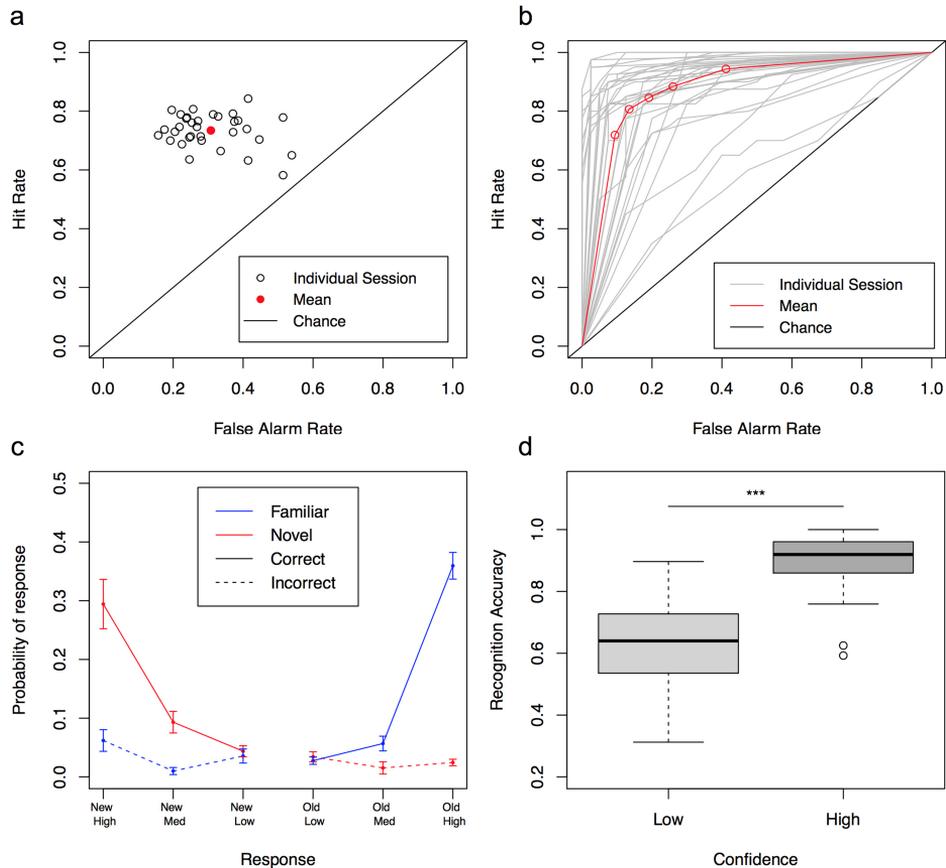


Figure 2.2: Recognition Performance. (A) Performance as a function of proportion of trials correctly and incorrectly identified. Each point is one session ($n = 33$); red point indicates the mean performance. (B) Behavioral Receiver Operating Characteristic (ROC) curve for individual sessions (gray) and average (red). Each data point is a different confidence level. (C) Response probabilities for familiar and novel, correct and incorrect items. Error bars represent \pm SE across subjects. (D) Normalized recognition accuracy was significantly higher in trials recognized with high confidence compared to low confidence trials. *** $p < 0.001$. P values are corrected for multiple comparisons.

= 97.9, $p = 0.06$, $\eta^2 = 0.07$, Figure 2.3 A). Two example trajectories are shown in Figure 2.3 B.

Participant's navigation was close to optimal after the learning session, al-

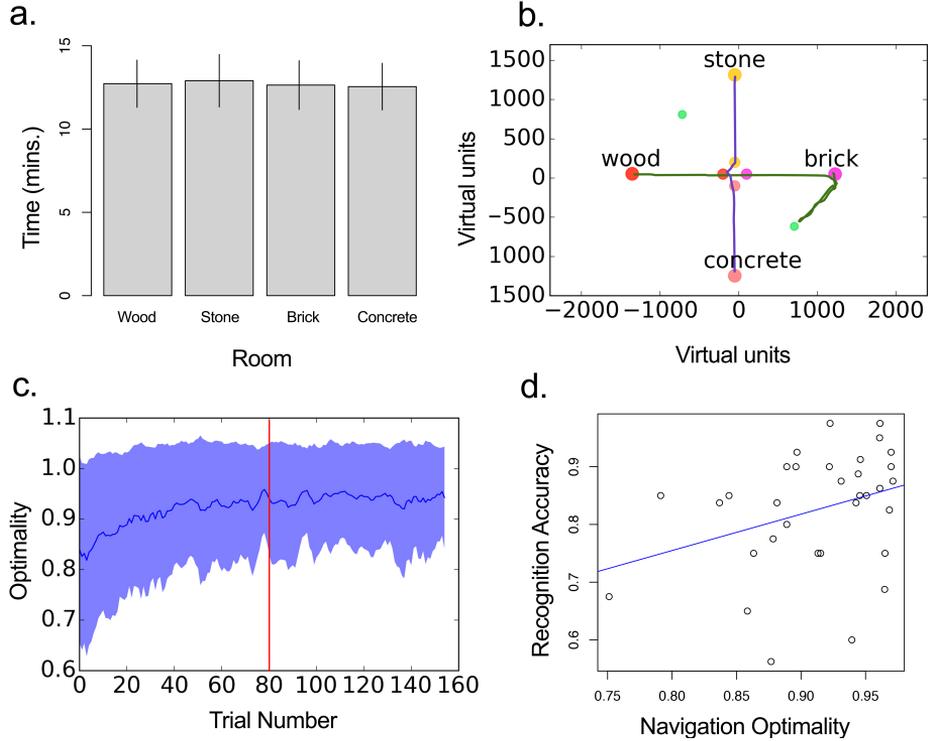


Figure 2.3: Navigation performance. (A) Mean time of all participants in each room. Error bars represent \pm SD across subjects. (B) Example trajectories from the same participant indicating different optimality values (green = 0.97, pink = 0.60). (C) Optimality in navigation as a function of trial number. Trial 80 marks the start of the testing block. Blue line represents mean optimality and shaded area the standard deviation. (D) Navigation optimality as a function of recognition accuracy. Blue line shows the least square fit.

though some learning also took place during the first trials of the encoding block (Figure 2.3 C). Mean optimality was higher in the testing block ($M = 0.91$, $SE = 0.01$) compared to the encoding block ($M = 0.87$, $SE = 0.009$, $t_{(32)} = 7.76$, $p < 0.01$, $d = 1.35$; Figure 2.3 C). The individual data revealed the different profile of responses observed across participants (Figure 2.5).

We aimed to assess the statistical dependency of navigation optimality and recognition accuracy. For this we calculated a mean optimality value for each session and participant. Neither optimality or recognition accuracy were

normally distributed (Shapiro Wilk’s normality test, $p < 0.05$). Therefore, we used the Spearman’s rank correlation coefficient. Results indicated that optimality in navigation and overall performance in the recognition test were positively correlated, $\rho_{(3753)} = 0.37$, $p = 0.03$, Figure 2.3 D.

We next assessed the relationship between the two variables by dividing subjects into those who scored high in navigation optimality ($>$ median of all subjects), and those that performed low ($<$ median). Recognition accuracy was not significantly different in the two groups $t_{(29)} = 1.5$, $p = 0.14$, $d = 0.53$.

2.3.3 Spatial context modulates recognition performance

The main objective of this research was to assess differences in performance related to the congruency of spatial context of items at encoding and retrieval. Target items in the retrieval block were presented in the same room and position on the wall with respect to their location when encoding took place (congruent trials), or in a different room and different position on the wall (non-congruent trials).

A repeated measures ANOVA model revealed a main effect of item condition (old congruent–old incongruent) in recognition performance, $F_{(32)} = 7.77$, $p = 0.01$, $\eta^2 = 0.19$. *Post hoc* analysis confirmed that accuracy in recognition was better for congruent compared to non-congruent trials (Congruent: $M = 0.87$, $SE = 0.01$, Non-congruent: $M = 0.81$, $SE = 0.02$, $t_{(32)} = 2.9$, $p = 0.01$, $d = 0.51$, Figure 2.4 A).

Given that the testing block included a recognition test at each trial, mean duration was significantly higher in the testing as compared to the encoding block (Encoding: $M = 28.67$, $SD = 3.75$, Testing: $M = 33.45$, $SD = 7.51$, $t_{(32)} = 4.1$, $p = 0.01$, $d = 0.71$). Since subjects navigated with different levels of optimality and that the order of presentation of items was randomized, the target item’s elapsed time between encoding and retrieval was different at each trial. To assess the influence of this factor in recognition performance, we split trials into those with short and long elapsed time (below and above

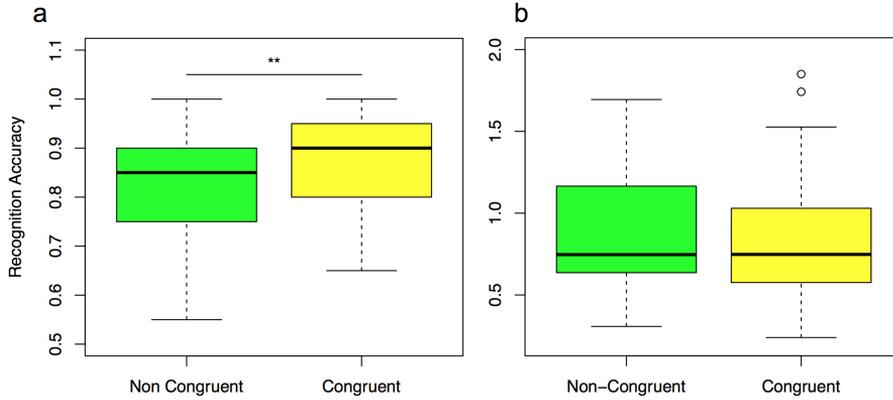


Figure 2.4: Recognition performance for congruent and non-congruent items. (A) Normalized accuracy in non-congruent and congruent trials. (B) Decision Time (DT) for non-congruent and congruent trials. ** $p < 0.01$. p values are corrected for multiple comparisons.

the median for each subject) and included this factor in our ANOVA model. We found a main effect of elapsed time on recognition performance $F_{(1,32)} = 4.89$, $p < 0.05$, $\eta^2 = 0.13$. This effect did not reach significance after Bonferroni correction in the *post hoc* analysis (Short: $M = 0.86$, $SE = 0.01$, Long: $M = 0.82$, $SE = 0.01$, $t_{(32)} = 2.23$, $p = 0.09$, $d = 0.38$. No interaction between elapsed time and item condition was found $F_{(1,32)} = 0.01$, $p < 0.89$, $\eta^2 = 0.0005$).

We next checked whether the observed differences in performance for congruent and incongruent items were confirmed in DT. Analysis showed a significant main effect of condition $F_{(2,64)} = 10.88$, $p < 0.01$. *Post hoc* analysis revealed that although DT was shorter for congruent items ($M = 0.87$, $SE = 0.09$), compared to non-congruent ($M = 0.98$, $SE = 0.11$), this difference did not reach significance after Bonferroni correction, $t_{(32)} = 2.9$, $p = 0.05$, $d = 0.4$ (Figure 2.4 B). New items, on the other hand, were recognized with significantly larger DTs than old congruent and old incongruent trials (new: $M = 1.2$, $SE = 0.11$); compared to old congruent $t_{(32)} = 4.56$, $p = 0.01$, $d = 0.79$; compared to old incongruent $t_{(32)} = 7.14$, $p = 0.01$, $d = 1.24$.

2.4 Discussion

According to the encoding specificity principle (Tulving and Thomson, 1973), human memory is improved when information available at encoding is also available at retrieval. Previous research has shown that the principle is valid in recognition memory (Smith and Vela, 2001), although in highly constrained experimental setups. Here, we approached the problem from the perspective of space and human spatial behavior. Using VR, we could generate encoding and retrieval conditions that are more likely to occur in the real world, and that are known to modulate memory in rodents (Rennó-Costa et al., 2010; Lu et al., 2013). In our setup, each item to be learned was associated with a unique spatial context, and active navigation was required to reach the items at encoding and retrieval. This allowed us to create a strong contextual association for each item, which included spatial and navigational aspects.

Our results confirm a significant modulation of recognition memory by incidental context. Recognition accuracy was significantly higher for items in which contextual information was congruent compared to those in which it was different. Furthermore, we identified a tendency for congruent items to be recognized in shorter DTs as compared to incongruent ones, although this difference did not reach significance after Bonferroni correction ($p = 0.05$).

These findings contribute to a long tradition of investigations that have explored the modulation of recognition memory by environmental context in experimental psychology. Indeed, early studies have reported mixed results on the effects of spatial context in recognition i.e., inexistent (Fernandez and Glenberg, 1985) or small (Smith, 1985; Murnane and Phelps, 1994). Our data confirms the current view that such effects exist (Smith and Vela, 2001), and we further quantify that recognition accuracy was 6% higher for items in which spatial position at encoding and retrieval was congruent compared to that of trials in which it was different (a bigger effect than the 2% reported for instance in Smith, 1985, for lists of words).

On the other hand, the analysis of trajectory data revealed that on average

subjects learned the maze throughout the experiment, which is reflected in the increased navigation performance during the testing as compared to the encoding block. Interestingly, we observed that navigation optimality and recognition accuracy were positively correlated. However, the observed variability in the individual data indicated that navigation optimality was differently linked to performance in the memory test across subjects (Figure 2.5). For instance, subject 15 navigated optimally (Mean optimality = 0.96) but had a recognition accuracy of 0.68, whereas subject 8 navigated similarly well (Mean optimality = 0.98), with an memory score of 0.975. The high inter-subject variability and the fact that some subjects performed poorly in the last trials of the encoding block suggests that participants used different strategies to navigate and did not learn the maze equally. Although the positive correlation we observe is consistent with a critical role of space in the association of items with their context (Nadel, 2008), the relationship of spatial learning and memory for spatialized items will require further investigation.

A final remark related to the spatial behavior analyses is that navigation performance affected the time elapsed between the encoding and retrieval blocks of the experiment. At an item level, the time elapsed between these two moments was dependent on spatial performance and on the order of presentation of stimuli, which was randomized. We controlled for this potential confound variable in our analyses and found that time elapsed did not significantly affected memory and did not interact with the modulation of recognition performance by spatial-context previously discussed.

In terms of overall accuracy, our results are consistent with several studies that have characterized human behavior in recognition memory experiments (Squire et al., 2007; Rutishauser et al., 2015). This can for instance be appreciated in the asymmetrical shape of the ROCs, the distribution of AUCs, the enhanced performance in high confidence trials as compared to low confidence ones, or in the faster DTs for familiar items as compared to new ones (Squire et al., 2007; Rutishauser et al., 2015).

Moreover, our results suggest that VR can be a powerful tool to investigate the modulation of memory by incidental context. Previous studies have questioned the validity of virtual environments for the study of spatial behavior and particularly route memory (van der Ham et al., 2015). Indeed, disembodied navigation does not capture key factors of navigation that affect memory, such as proprioceptive or vestibular information (Chrastil and Warren, 2012). Nonetheless, it is likely that the effects we observe are not related solely to the visual information associated with the items, but to a broader context which includes spatial and navigational aspects. It has been shown that the brain systems for navigation including Grid and Place cells activate during stationary VR navigation (Ekstrom et al., 2003; Jacobs et al., 2013). Moreover, place cells that fire when specific items are encoded during navigation in Desktop VR also discharge when these items are retrieved in free recall (Miller et al., 2013b). We speculate that the activity of place cells representing space might have contributed to a stronger context effect in our setup, even in the absence of real movement. Indeed, even if subjects were not actually moving when the stimulus was presented, each item was shown in a specific place, i.e., a room, probably encoded by place cells in the hippocampus. The specific contribution of embodiment in the modulation of memory will remain to be determined in future experiments.

In future research, we also aim to investigate the neural signatures of the behavioral effect we observe in the human hippocampus, a key structure in the binding of items and context (Bird and Burgess, 2008; Nadel, 2008; Dede et al., 2013). Indeed, previous research conducted with intracranial recordings in humans has shown increases in hippocampal gamma power for associative vs. non-associative recognition in a non-spatial setup (Staresina et al., 2016). Moreover, neurons in the hippocampal formation have been reported to encode several components of recognition tasks, such as object categories, novelty/familiarity and confidence (Rutishauser et al., 2015). Hippocampal cells have also been linked to the encoding of recollection and familiarity—both key cognitive processes that are thought to underlie recognition memory (Merkow et al., 2015).

In summary, by extending the study of recognition memory to the domain of spatial behavior, we report for the first time human behavioral data expressing the link between space and recognition memory performance. This is a novel finding that extends our current understanding of recognition memory, and could be used in the design of novel educational paradigms (Pacheco et al., 2014).

2.5 Supplementary Information

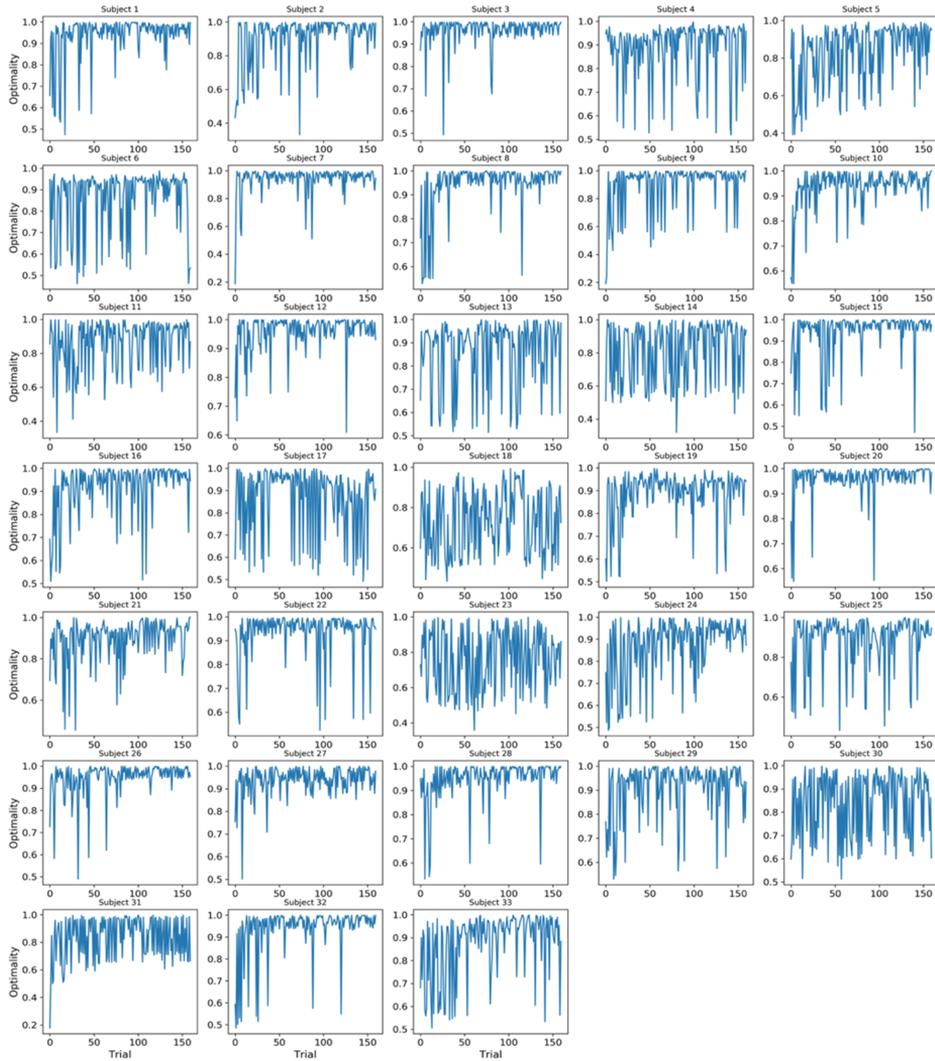


Figure 2.5: Navigation Optimality per subject. Each plot is the optimality curve (y axis) plotted as a function of trial number (x axis). The average data can be found in Figure 2.3 C. The relation of optimality and recognition accuracy is shown in Figure 2.3 D.

Coordinated representational reinstatement in hippocampus and lateral temporal cortex

After demonstrating the modulation of human recognition memory by environmental context (Chapter 2), we explored the physiological signatures of the observed effect in the brain. We conducted the same Virtual Reality (VR) test described in the previous chapter with a group of seven patients implanted with intra-cortical electrodes for epilepsy monitoring. We present our analysis pipeline, based on Representational Similarity Analysis (RSA, Kriegeskorte et al., 2008), and results, which show a coordinated reinstatement of oscillatory patterns in the hippocampus and the lateral temporal cortex during context-dependent memory retrieval.

The text presented here is part of a manuscript entitled “Coordinated representational reinstatement in hippocampus and lateral temporal cortex”, which will be submitted to a specialized jour-

nal on the neurophysiology of memory during 12/17. It follows the journal's *report* structure which includes an extended abstract, results, discussion and methods section. The extended abstract reads:

It is believed that acquisition and retrieval of memories in the hippocampus is strongly dependent on context (Tulving and Thomson, 1973; Staudigl and Hanslmayr, 2013). In addition, it has been shown that the retrieval of memory leads to a reinstatement of a dynamical state that occurred during acquisition (Yaffe et al., 2014; Zhang et al., 2015; Staresina et al., 2016). From this we can predict that the physiological signatures of reinstatement in the hippocampus should also show a systematic context-dependent modulation. In humans, evidence supporting this hypothesis comes from the observation of increased reinstatement of broadband oscillatory activity for the retrieval of source as compared to item memory in the hippocampus (Staresina et al., 2016). However, whether contextual information itself modulates hippocampal reinstatement during the retrieval of episodic memories is unknown. Besides, it is not clear how the balancing between item and context information occurs and whether it is solely dependent on hippocampal processes. For instance, it has been suggested that hippocampal memory critically depends on an interaction with the neocortex (Eichenbaum and Cohen, 2004). Yet the interaction of local reinstatement in the hippocampus and cortical regions during memory retrieval has not been investigated before. To address these issues, we studied item and context-specific reinstatement of broadband oscillatory power in the hippocampus and the lateral temporal cortex (LTC). Patients implanted with intra-cortical electrodes performed a Virtual Reality (VR)-based recognition memory test (Pacheco et al., 2017). By manipulating the spatial-context associated with items at encoding and retrieval we could analyze

the patterns of brain activity in the recorded intracranial EEG (iEEG) data. Our results show increased reinstatement of hippocampal activity for congruent as compared to incongruent trials. The cortical electrodes, on the contrary, did not reveal any context effects but rather two clusters of significant encoding-retrieval time pairs in the comparison of item information. LTC reinstatement was also higher for high as compared to low confidence trials from ~ 1 -2 seconds after stimulus onset at retrieval and ~ 2 -3 at encoding. Critically, correlations between mean activity in the congruent-incongruent hippocampal cluster and the LTC confidence cluster were systematically positive in all our patients, and significantly greater than zero at the group level. Taken together, our findings show for the first time the neurophysiological signature of context-dependent memory in humans, suggesting that memory, as the conjunction of spatial context and distinct items, is constructed in the interaction between the neocortex and the hippocampus.

3.1 Results

Recording simultaneously from the hippocampus (HC) and lateral temporal cortex (LTC) of epilepsy patients ($n=7$), we investigated the electrophysiological patterns supporting the reinstatement of neural representations of individual items and of their spatial contexts. Participants first navigated through a virtual maze and were presented discrete images once they visited one of four rooms. Subsequently, they were tested for their memory of those items, during navigation in congruent and incongruent spatial-context conditions (congruent: same position at encoding and retrieval; incongruent: different position at encoding and retrieval; Methods; Figure 3.1A). We observed that in this task the participants' memory performance was significantly above chance (Area Under the Curve, $AUC = .73 \pm .21$, mean

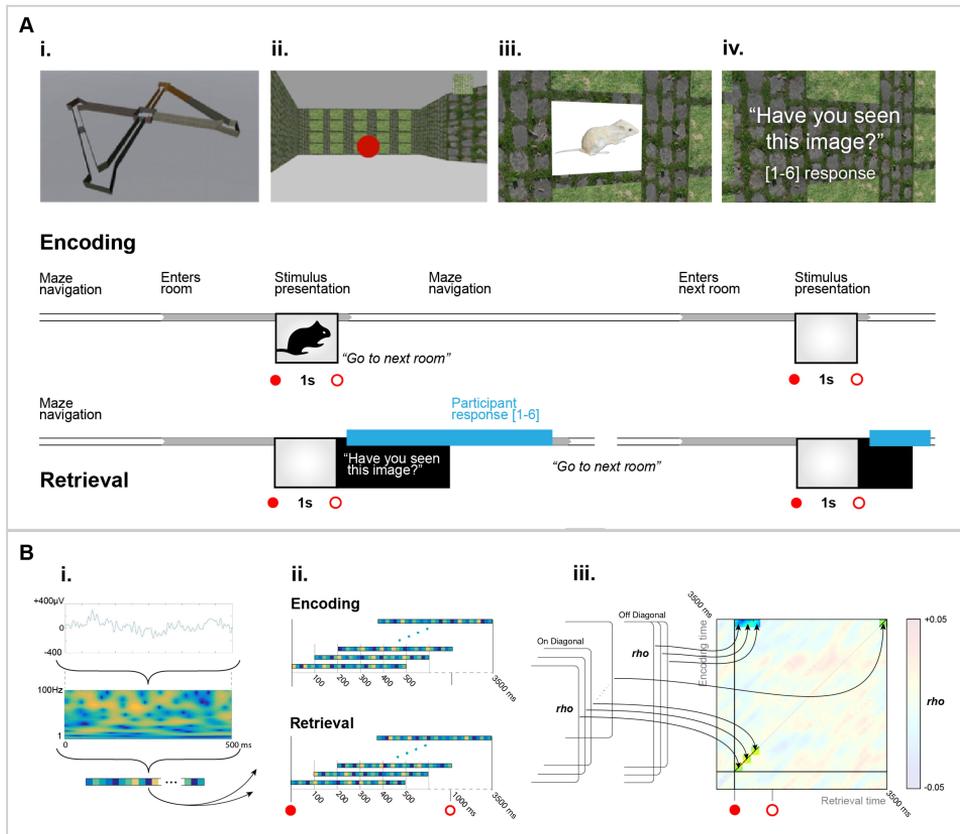


Figure 3.1: Task description and reinstatement analysis. A) Top: i) Spatial layout of the maze. ii) Participants visited specific rooms and approached a viewing location (red sphere). iii) An item was presented for one second on a 5x4 matrix on the wall. iv) At retrieval, an image was presented again during navigation, either in the same position as before (i.e., same room and matrix, congruent trial) or in a different position (incongruent trial). After stimulus presentation, participants were tested on their recognition memory for the specific item using confidence ratings. Bottom: Timeline of one example trial during the encoding and retrieval blocks of the experiment. B) Representational similarity analysis. i) A pattern of relative changes in oscillatory power after stimulus onset was extracted in 500 ms time windows (44 frequencies in total, 1-100 Hz range), and the power spectrum was concatenated into a one-dimensional feature vector. ii) The representational pattern was extracted at every 100 ms (80% of overlap), during all encoding and retrieval epochs. iii) A reinstatement map was produced by calculating the Spearman's correlation for each encoding-retrieval time pair across conditions. The diagonal in the map shows non-lagged correlations.

\pm sd, see Supplementary Figure 3.7). In order to quantify the the similarity of neural representations during encoding and retrieval we compared epochs of brain activity through representational similarity analysis (RSA, Kriegeskorte et al., 2008). We focused specifically in HC (Staresina et al., 2016) and LTC electrodes (Figure 3.2). In short, we calculated Spearman's correlations across time (window size of 500ms, overlapping by 100ms) and frequency (power of 44 frequency values between 1 and 100Hz) over multiple encoding/retrieval time windows (Figure 3.1B). Results were corrected for multiple comparisons at the cluster level using non-parametric surrogate statistics (Maris and Oostenveld, 2007; see Methods).

3.1.1 Reinstatement of item-context associations in the hippocampus

We first assessed the reinstatement of the physiological signature of item / context associations and of individual items in HC and LTC. In the HC, we observed a significantly larger Encoding-Retrieval Similarity (ERS) in congruent trials as compared to incongruent ones ($ERS_{(\text{item same, context same})}$)

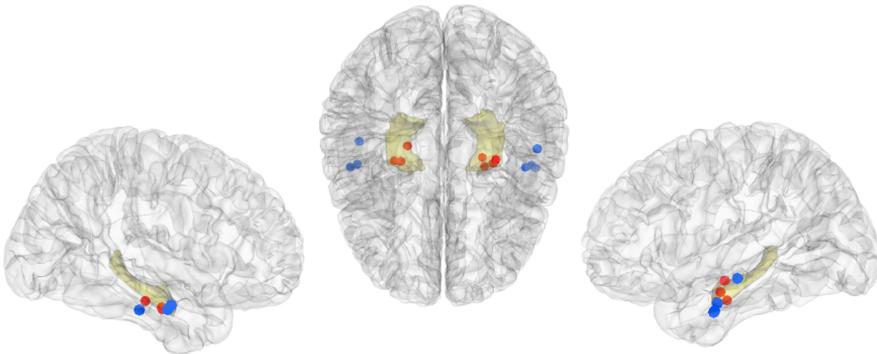


Figure 3.2: Electrode placement. An electrode implanted laterally in the Medial Temporal Lobe (MTL) was selected for each patient. The deepest contact located in the hippocampus (red) and the more distal one (centered in cortical grey matter) in the LTC (blue) were chosen. Image shows all contacts from all patients in common MNI space.

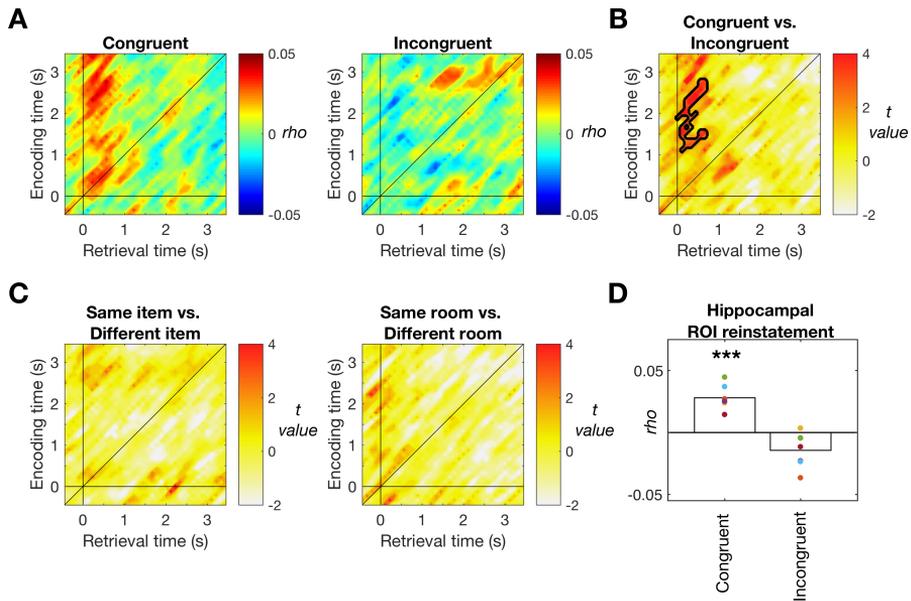


Figure 3.3: Reinstatement of item-context associations in the hippocampus. A) Reinstatement map for congruent (left) versus incongruent (right), trials in the hippocampus. B) t -map for the congruent vs. incongruent comparison revealing a cluster of significant differences from ~ 1.25 to 2.75 seconds at encoding to ~ 0 to $.75$ seconds at retrieval ($p_{(\text{corr})} < .05$, outlined in black). C) Item (left) and context (right) comparisons of activity at the hippocampal electrode, revealing no significant differences (all $p > .5$). D) Mean reinstatement for all encoding-retrieval time pairs that exhibited significant differences in the congruent - incongruent comparison (ROI, outlined in black in panel B; *** = p -values are significantly different from 0 at $p < .001$).

$> \text{ERS}_{(\text{item same, context different})}$; $p_{(\text{corr})} < .05$; Figure 2A,B). This enhanced ERS effect was significant between $\sim 1.25 - 2.75$ s at encoding and $\sim 0 - .75$ s at retrieval, suggesting both time-shifted and time-compressed reinstatement (Yaffe et al., 2017) with a compression factor of around 2 (i.e., cluster duration ~ 1.5 s during encoding and $\sim .75$ s during retrieval). By contrast, we did not find any evidence for item reinstatement: ERS did not differ when the same item was encoded and retrieved ($\text{ERS}_{(\text{item same, all contexts})}$) as compared to when one item was encoded and another item retrieved ($\text{ERS}_{(\text{item different, all contexts})}$; all clusters, $p > .5$; Figure 2C, left). This ERS congruency effect cannot be fully accounted for in terms of the differences between rooms, i.e. context: when we compared ERS involving same or different rooms regardless of items ($\text{ERS}_{(\text{item all, context same})}$ vs. $\text{ERS}_{(\text{item all, context different})}$), we did not observe any significant cluster (all clusters, $p > .1$; Figure 2C, right).

Figure 3.3D summarizes mean ERS in the cluster of interest for congruent and incongruent trials (Figure 3.3A). Average ERS values in this Region of Interest (ROI) were significantly higher than zero in the congruent trials ($t_{(6)} = 6.93$, $p < 4.44 \times 10^{-4}$), but not in the incongruent ones. In all other conditions (i.e., same item, different item, same room, and different room), reinstatement was not statistically different than what would be expected by chance (all $p > .05$, t -test against zero, Bonferroni corrected). Taken together, our results demonstrate that during recognition the anterior hippocampus reinstates a dynamic pattern of oscillatory power when items and contexts of encoding and retrieval match, and that this reinstatement is time warped, i.e., advanced in time and compressed.

3.1.2 Reinstatement of items but not context in the lateral temporal cortex

We also investigated the reinstatement of items, contexts, and item/context-associations in LTC and observed a marked difference with the hippocampal iEEG (Figure 3.4). We observed two significant item reinstatement clusters independent of context ($\text{ERS}_{(\text{item same, all contexts})} > \text{ERS}_{(\text{item different, all contexts})}$);

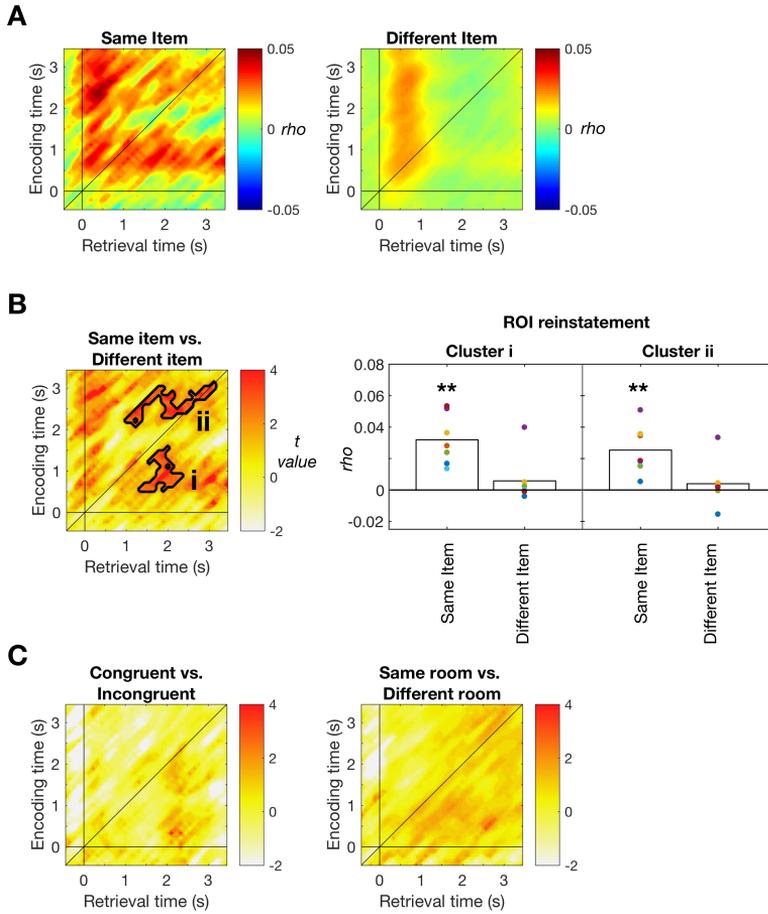


Figure 3.4: Reinstatement of items in lateral temporal cortex. A) Left: Grand average of encoding-retrieval similarity across all items (“same item” correlations). Right: Grand average of correlations of activity during encoding of each item with activity during retrieval of each other item (“different item” correlations). B) Left: T -map contrasting “same item” versus “different item” correlations, revealing two significant clusters (cluster i: ($p_{\text{corr}} < .05$); cluster ii: ($p_{\text{corr}} < .05$); black outlines). Right: Bar plots show mean reinstatement in these clusters for same item trials and different item surrogates (** = p -values are significantly different from 0 at $p < .01$). C) Cluster-corrected t -map for the congruent versus incongruent comparison (left) and the same room vs. different room comparison (right) in the lateral temporal cortex revealed no significant encoding/retrieval time pairs.

$p_{(\text{corr})} < .05$; Figure 3.4A). In particular, encoding activity in the time windows 1.25 - 1.75s and 2.25 - 3s was reinstated during a retrieval time window between $\sim .5$ - 2s.

Average ERS in the same item condition was significantly higher than zero for both clusters (cluster i: $t_{(6)} = 5.67$, $p = .001$; cluster ii: $t_{(6)} = 4.0$, $p = .007$, Figure 3.4B). In contrast, we did not observe any item-context association effect as in the hippocampal ERS analysis that showed higher reinstatement for congruent trials (all clusters, $p > .1$; Figure 3.4C left). As in the hippocampus, no cluster survived the room-specific contrast (all clusters, $p > .05$; Figure 3.4C right).

3.1.3 Functional relevance of reinstatement in lateral temporal cortex

Given the distinct effects of reinstatement in both hippocampus and LTC we next explored if reinstatement is related to performance. Since participants correctly remembered most of the items, we could not directly contrast hit vs. miss trials. Instead, we compared high confidence with lower-confident ones (see also Rutishauser et al., 2015). One out of seven participants reported high confidence to all responses and was therefore excluded from this analysis. Whereas we did not observe significant differences in congruency or item reinstatement for high and low-confidence trials in the hippocampus (Figure 3.5C), the LTC showed higher levels of reinstatement for high-confidence trials as opposed to low confidence ones ($\text{ERS}_{(\text{high confidence, all items})} > \text{ERS}_{(\text{low confidence, all items})}$; $p_{(\text{corr})} < .05$). This confidence effect on the ERS appeared in an encoding time window from 2.5 to 3s and a retrieval time window from 1 to 2s (Figure 3.5A, B). The ERS cluster partially overlapped with one of the clusters showing item-specific reinstatement in the LTC (Figure 3.4B). The reinstatement effect of high-confidence trials was significantly larger than zero ($t_{(5)} = 3.64$, $p = .01$), while it did not differ from zero for low-confidence trials ($t_{(5)} = -1.62$, $p = 1.65$; Figure 3.5D).

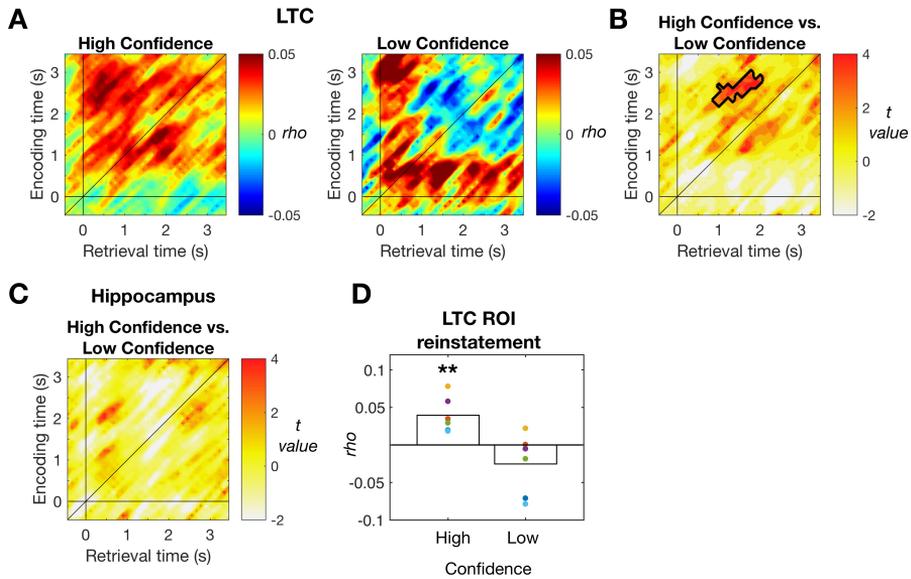


Figure 3.5: Functional relevance of reinstatement in lateral temporal cortex. A) Reinstatement map (same vs. different item comparison) for high and low confidence trials. B) T -map in the confidence comparison revealed a significant cluster from 1 to 2 seconds at retrieval and 2 to 3 seconds at encoding ($p_{\text{corr}} < .05$). C) No differences in the confidence comparison were found in the hippocampus. D) Average reinstatement for the significant cluster observed in the confidence comparison (black outline in panel B) in the LTC. Reinstatement values in high confidence trials were all positive and significantly different from 0 (** = p -values are significantly different from 0 at $p < .01$).

In summary, the results presented thus far demonstrate a double dissociation between reinstatement of item representations and of item-context associations, both spatially — with item reinstatement occurring in the LTC and item-context reinstatement in the hippocampus — and temporally, with item-context reinstatement occurring earlier during retrieval than item reinstatement. In our final analysis, we assessed whether these two types of reinstatement were coupled across trials, by correlating the magnitude of item reinstatement in the LTC with the magnitude of item-context reinstatement in the HC.

3.1.4 Coordination of representational reinstatement between hippocampus and lateral temporal cortex

In order to identify the inter trial LTC HC coupling, we focused on the cluster showing item-context reinstatement in the HC, and the cluster showing behaviorally relevant item reinstatement in the LTC (Figure 3.6A, left). We defined a rectangular ROI surrounding the two clusters, from 0 to 0.5s at encoding and 1 to 2.75s at retrieval in the HC, and from 2.25 to 3s at encoding and 1 to 2s at retrieval in the LTC. We correlated mean activity in all trials from a specific contrast in both clusters, which resulted in unique “correlation of correlations” value for each subject (Methods). At the group level, this measure of coordinated reinstatement was consistently larger than chance (t -test of Fisher z -transformed ρ -values against zero: $t_{(6)} = 4.98$, $p < .01$), suggesting that trials in which hippocampal reinstatement was high were also characterized by high LTC reinstatement. This effect was mainly driven by congruent trials: i.e. we still found consistently positive correlations when we restricted our analysis only to congruent trials ($t_{(6)} = 2.77$; $p < .05$), but not when we only analyzed incongruent trials ($t_{(6)} = 1.15$, $p = .2$; Figure 3.6A, right for the all items comparison). Taken together, these results suggest that the distinct ERSs of the LTC and HC are also reinstated in combination and specific temporal order in congruent high confidence trials.

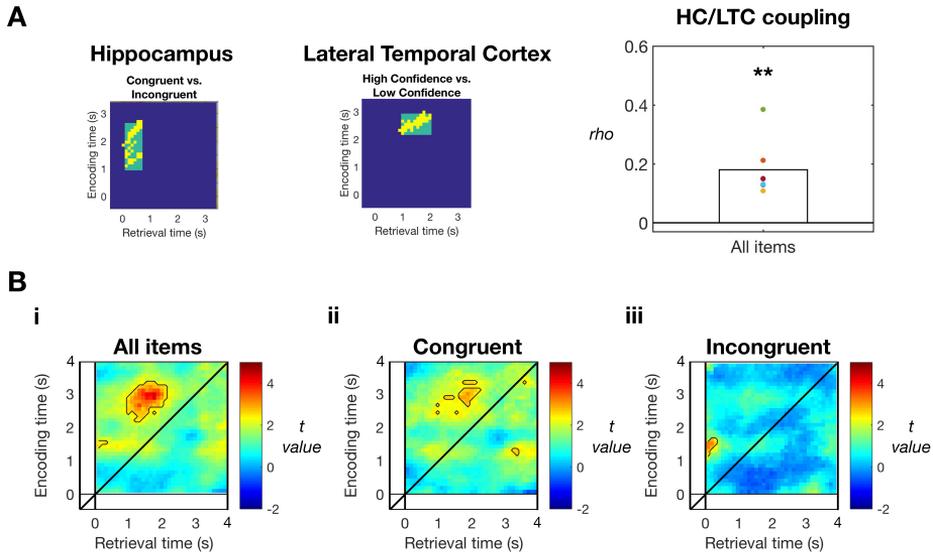


Figure 3.6: Coordination of representational reinstatement between hippocampus and lateral temporal cortex. A) Left: A temporal region of interest (ROI) was defined in the reinstatement maps of the hippocampus and LTC based on the significant clusters found in the congruent-incongruent and confidence contrasts respectively. Right: correlation between reinstatement at the two regions when including all (same-item) trials. B) Correlation map between the hippocampal cluster and all encoding-retrieval time pairs in the LTC (with a cluster equally sized as in panel A, bottom left). The map shows t -values when testing correlations against zero for all (left) congruent (middle) and incongruent (right) trials. Areas in which values reached significance at $p < .05$ are outlined. A cluster of significant values is observed in the all items comparison (left panel), which overlaps with the cluster observed in the confidence comparison in the same brain region.

In order to assess whether these results are specific to the temporal regions of interest we selected, we performed the same trial-by-trial correlation analysis, sliding the LTC rectangular ROI over all encoding/retrieval time pairs, using the HC ROI as a seed (Methods). Correlations were significantly different from zero only in a single cluster that overlapped with the LTC ROI chosen a priori ($p < .05$, outlined in black in Figure 3.6Bi, results are uncorrected for multiple comparisons). Again, results were mainly driven by congruent (Figure 3.6Bii) rather than incongruent trials (Figure 3.6Biii), further confirming our observation of HC LTC coupling.

3.2 Discussion

We exploited representational similarity analyses (Kriegeskorte et al., 2008) on time-frequency transformed intracranial EEG data from HC and LTC of presurgical epilepsy patients. We observed associate reinstatement of item-context information in the HC preceding, and correlated with, item reinstatement in the LTC. Our data are consistent with a growing body of intracranial EEG studies on representational reinstatement, either distributed across electrodes in the brain or at individual electrodes (Yaffe et al., 2014; Zhang et al., 2015; Staresina et al., 2016). Specifically, previous work has shown reinstatement of item information in neocortex (Yaffe et al., 2014; Jang et al., 2017) and increased reinstatement in the hippocampus for source as opposed to item memory (Staresina et al., 2016). However, our results are the first to demonstrate how reinstatement of different representational features is coordinated between hippocampus and neocortex and generalize these effects to tasks where the subjects are freely behaving in a VR environment.

Our analysis in HC showed important differences in timings of reinstatement with respect to previous work. Indeed, by extending the encoding-retrieval time space in which we evaluated ERS we could capture significant clusters seconds after the stimulus was presented. In Staresina et al. (2016), clusters of reinstatement were observed from $\sim.5$ to 1s at encoding and ~ 1 to

1.5s retrieval. We observed reinstatement in the hippocampus at the onset of the stimuli at retrieval and after 1s in encoding time in the congruent-incongruent contrast. Item and confidence reinstatement in the LTC were also observed seconds after stimulus presentation. It is likely that the specific characteristics of our setup modulated the timings of reinstatement. Indeed, information related to specific contexts was present permanently in our paradigm, as opposed to other setups in which context has been operationalized under more constrained conditions.

A second important issue relates to the sequential order of reinstatement across brain regions. Although from the results presented in this study we cannot infer directionality, the fact HC reinstatement precedes, rather than follow LTC's reinstatement suggests a causal link between the two regions. However, whether cortical reinstatement is triggered by the hippocampus will remain to be determined in future research.

A third important point is related to the role of specific frequencies in driving reinstatement. Previous work has reported that ERS requires the rich information profile carried by a wide range of frequencies, as observed in the absence of the effect when calculated by considering one frequency band in isolation (Staresina et al., 2016). On the other hand, global reinstatement of spatial context has been found to happen mostly in the gamma band (Zhang et al., 2015). We performed a frequency specific analysis to assess ERS when considering one specific band at a time. Our results confirmed that local reinstatement in the hippocampus could not be captured by any of the traditional bands alone (no cluster survived multiple comparisons correction in the congruent incongruent contrast). This confirms that event-specific hippocampal reinstatement capitalizes on information encoded in a wide range of frequencies.

Finally, our results of no room-specific reinstatement in HC seem at odds with the traditional role assigned to the hippocampus in spatial navigation. Previous studies using high-resolution fMRI have shown accurate prediction of the position of humans in an environment from the pattern of activity

in his hippocampus (Hassabis et al., 2009). These results might be partially explained by the epochs of activity we selected — which were always linked to the presentation of an item. Whether room-specific information can be decoded in other brain epochs of activity, or whether information related to future trajectories (Brown et al., 2016) can be extracted from the hippocampal iEEG will remain to be determined in future research.

3.3 Methods

3.3.1 Participants

Seven epilepsy patients (2 males, 21-38 years) who had been surgically implanted with depth electrodes as part of their diagnostic assessment of surgical treatment for medically refractory epilepsy participated in our experiment. The test was initially conducted with 9 patients, but in 2 of them, the onset of the epileptic seizure was found in the hippocampus, and they were therefore excluded from the analyses.

3.3.2 Task description

The experimental protocol has been previously conducted with a group of 33 healthy human subjects (Pacheco et al., 2017). We briefly describe here the methodology of the experiment and refer the reader to this publication for further details on the behavioral analysis.

Patients were asked to navigate a virtual maze comprising a central and four satellite rooms. Each room had a unique visual texture on its walls (i.e., concrete, stone, brick, and wood). In each trial, patients were presented a texture and asked to navigate to the corresponding room. Each room contained a wall matrix of $5 \times 4 = 20$ images. During encoding, once they arrived in each room, they were presented with one specific image (presentation time, 1s) and were asked to memorize it. Subjects encoded a total of 40 images. During retrieval, patients were asked to indicate whether they had seen the image during encoding, using a 6 points confidence scale—from

1 (Sure unfamiliar) to 6 (Sure familiar) (Squire et al., 2007). Participants saw the 40 encoding items again, randomly intermixed with 40 new items. Half of the old items were shown in the same room and at the same position on the wall matrix as during encoding (congruent items), while the other half were shown in a different room and at a different position (incongruent items).

All items were extracted from a publicly available dataset (Moreno-Martínez and Montoro, 2012). From the 360 objects in that dataset, 160 items were selected from eight semantic categories (food, furniture, human body, musical instruments, buildings, tools, clothes and animals). For each subject separately, a subset of 80 images was selected randomly from this pool of 160 images, and assigned (again randomly) to specific conditions. In total, 20 images were assigned to the congruent condition and 20 to the incongruent condition.

Before the start of the experiment, subjects performed a training session in which they could gain spatial knowledge on the maze and familiarize with the interface. The task in the training session was to reach 10 rooms one after the other (without encoding items). The starting position for the first trial in each block was set to the central room for all participants. The sequence of rooms to visit was randomized. Patients performed the task on a 17" portable computer while sitting in their hospital bed. They controlled navigation with a joystick. The VR application was created using the Unity3D game engine (Unity Technologies, San Francisco, CA, USA).

3.3.3 Intracranial EEG analysis

Electrophysiology

Recordings were performed using a standard clinical EEG system (XLTEK, subsidiary of Natus Medical) with 500 Hz sampling rate. A unilateral implantation was performed in all patients, using 7 to 10 intracerebral electrodes (Dixi Médical, Besançon, France; diameter: 0.8 mm; 5 to 15 contacts,

2 mm long, 1.5 mm apart) that were stereotactically inserted using robotic guidance (ROSA, Medtech Surgical, Inc).

Electrode selection

Precise location of electrodes was achieved by our clinical team at the Hospital Del Mar (Barcelona, Spain). Targeted regions varied across patients for clinical reasons, but in all patients included the anterior hippocampus. The lateral implantation schema usually included 1-3 contacts points within the hippocampus per electrode, and 1-3 contacts in the lateral temporal cortex located in grey matter. We selected the two deepest contacts in the hippocampus and subtracted their activity to obtain a bipolar reference. In the LTC, we chose the contact point most centered in grey matter and subtracted the activity from the closest contact located distally to obtain a bipolar reference. The presence of specific contacts within the hippocampus and LTC was confirmed via careful examination of the MRI and CT scans. Electrode locations in real space as captured by the scans were converted to MNI coordinates using 3D slicer (www.slicer.org, Pieper et al., 2004), following the method described in Principe et al. (2017).

Spectral Power

We band-pass filtered the signal at the selected electrodes from 1 to 200 Hz using EEGLab (Delorme and Makeig, 2004). Before decomposing the signal, we binned the data into 10 seconds epochs centered around stimulus onset in the encoding and retrieval phase of the experiment. We chose a long window to avoid edge artifacts during wavelet decomposition. We decomposed the signal using complex Morlet Wavelets (number of cycles = 7) in 1Hz steps for the frequency range between 1 and 29Hz, and in 5Hz steps for the 30-100Hz range. We then visually inspected the 40 spectrograms together with the raw signal at encoding and retrieval for each subject independently to remove noisy epochs. Number of trials removed varied depending on the quality of the signal. In total, the number of trials included in the analysis was 34.71 ± 5.9 (mean \pm standard deviation). In the congruent condition,

of a maximum of 20 encoding retrieval time-pairs, 17.4 ± 2.9 were included. In the incongruent condition of 17.2 ± 3.0 were included. In the high confidence condition, a total number of 23 ± 9.8 encoding-retrieval time-pairs was included, and 10.7 ± 8.4 in the low confidence condition.

The resulting time-series of frequency specific power were then decibel transformed by taking as a reference the activity from a baseline period of -500 milliseconds until stimulus onset. The selection of the baseline was based on (Staresina et al., 2016).

Reinstatement analysis

We quantified the similarity of neural representations during acquisition and testing by comparing epochs of brain activity at HC and LTC electrodes through Representational Similarity Analysis (RSA, Kriegeskorte et al., 2008). As in Staresina et al. (2016), we used the Spearman’s correlation of broadband oscillatory patterns of activity across time, resulting in a measure of ranked similarity between two different moments at the same electrode. To assess the reinstatement of activity in specific trials, we first defined a 500 milliseconds time window in which we included the decibel corrected power changes from 1 to 100 Hz (1 Hz steps from 1–29 Hz, 5-Hz steps from 30–100 Hz) relative to a 500 milliseconds pre-stimulus baseline window. Given the sampling rate of the data (500Hz), a representational pattern consisted of 44×250 values which were concatenated into a one-dimensional vector for correlation analysis. Using a 100ms sliding window we calculated the correlations between the moments of encoding and retrieval across time. Similar to Staresina et al. (2016) and Yaffe et al. (2014), we compared not only the activity at the same time points at encoding and retrieval but correlated all encoding times with all retrieval times. This resulted in an encoding \times retrieval reinstatement map for each trial including lagged (off-diagonal) and non-lagged (on-diagonal) correlations (Figure 3.1C). The obtained reinstatement maps were subsequently Fisher-z transformed for statistical analysis and contrasted via paired-samples *t*-tests across conditions of interest.

Cluster-based permutation statistics were used to correct for multiple com-

parisons at the group level. Basically, for each contrast, we created a null hypothesis distribution of ERS values by permuting for each subject independently the labels of the conditions identifying the average reinstatement maps 1000 times. Paired t -tests were then applied for each encoding and retrieval time-pairs now on the shuffled data. We computed a distribution of cluster size by taking the sum of the t -values of the biggest cluster in each permutation. We only considered significant those contiguous encoding-retrieval time-pairs which length exceeded that of the 95% of the distribution of cluster sizes ($p < .05$; Maris and Oostenveld, 2007).

Interaction analysis

To assess whether reinstatement in the hippocampus and lateral temporal cortex were coordinated, we first defined two regions of interest (ROIs) in the reinstatement maps of the hippocampus and the LTC in the congruent-incongruent and confidence contrasts respectively. We created a rectangular mask over the reinstatement map whose limits were defined by the encoding-retrieval time pairs of the significant cluster. For each subject independently, we created two vectors in which we included the mean reinstatement observed in these rectangular ROIs in each contact at every trial. Note that one of the vectors was formed by the mean encoding-retrieval similarity values from the HC contact in the HC ROI and the other by mean reinstatement values from LTC in the LTC ROI. We used Spearman's ρ to assess the correlation of the two sets of values, obtaining one "correlation of correlations" value per subject across trials. We then Fischer z -transformed these scores and performed a t -test against zero across subjects separately for all (same-items), congruent and incongruent trials.

To address the specificity of the correlations in encoding-retrieval time, we performed the same analysis by sliding the LTC rectangular ROI over the whole encoding time x retrieval time space, using the hippocampal cluster as a "seed". We color coded the results over a new encoding time x retrieval time map with t -values obtained from the comparison of correlations against zero.

To correct for multiple comparisons, we generated a null hypothesis distribution by randomly shuffling the labels of the HC and LTC contacts and repeating the procedure 1000 times. For each iteration, we calculated the sum of t -values from the biggest cluster of contiguous encoding-retrieval time-pairs showing correlations significantly greater than zero. This gave us a distribution of t -values under the null hypothesis; then, we only considered significant the observed clusters whose summed t -values were above the 95% of the generated distribution.

3.4 Supplementary Figures

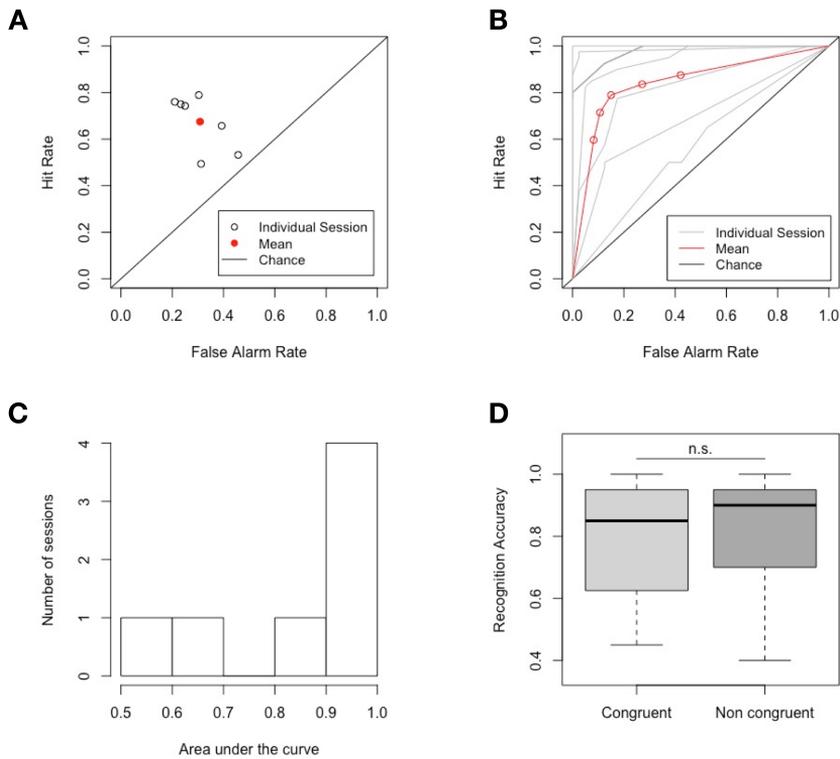


Figure 3.7: Behavioral Results. A) Performance as a function of proportion of trials correctly and incorrectly identified. Each point is one session ($n = 7$); red point indicates the mean performance. B) Behavioral Receiver Operating Characteristic (ROC) curve for individual sessions (gray) and average (red). Each data point is a different confidence level. C) Histogram of the AUCs. D) Recognition accuracy (% correct) for congruent and non-congruent trials.

Long-term spatial clustering in free recall

In previous chapters, we investigated the role of spatial context in the modulation of human recognition memory from a behavioral and neurophysiological perspective. However, space has also been shown to modulate the *structure* of memory, i.e., the associations between items in long-term storage. In this section, we examine whether the order in which participants report their answers in free recall is determined by the distance between items during navigation. We assess whether the tendency of participants to cluster their responses along a spatial dimension relates to the stability of memory and to forgetting, and study the dependency of spatial clustering scores on active navigation.

This chapter reproduces the content of a manuscript entitled “Long-term spatial clustering in free recall”, currently in press at *Memory*. The abstract reads:

We explored the influence of space on the organization of items in long-term memory. In two experiments, we asked our participants to explore a virtual environment and memorize discrete items presented at specific locations. Memory for those items

was later on tested in immediate (T1) and 24 hours delayed (T2) free recall tests, in which subjects were asked to recall as many items as possible in any order. In experiment 2 we further examined the contribution of active and passive navigation in recollection dynamics. Results across experiments revealed a significant tendency for participants to consecutively recall items that were encountered in proximate locations during learning. Moreover, the degree of spatial organization and the total number of items recalled were positively correlated in the immediate and the delayed tests. Results from experiment 2 indicated that the spatial clustering of items was independent of navigation types. Our results highlight the long-term stability of spatial clustering effects and their correlation with recall performance, complementing previous results collected in immediate or briefly delayed tests.

4.1 Introduction

In a traditional free recall experiment, participants are presented with a list of items and then asked to recall as many as possible in any order. Typically, subjects' responses are not randomly structured, but organized along a number of dimensions or attributes of the studied items. For instance, successive recalled items are more likely to be from neighboring serial positions in the study list (Kahana, 2012). The same "chunking" of items at retrieval is observed when stimuli are proximal in semantic space (Polyn et al., 2009).

In the domain of spatial memory, it has been shown that when items are studied in the space (e.g., encountered during navigation in a virtual reality scenario), Euclidean proximity between them is a strong predictor of the order in which they will be later on recollected in free recall, irrespective of their distance in other dimensions (Miller et al., 2013a,b).

These pioneering spatial clustering studies have increased our understanding on the relationship of space and memory in the human brain, highlighting

the role of distance in the structuring of items, and complementing a long tradition of investigations that have studied spatial-context effects without considering navigational aspects (Smith and Vela, 2001). On the other hand, spatial clustering studies have open novel questions. For instance, a relevant aspect is related to the persistence of the clustering effects over time. Theories have proposed that different types of memories involve different forms of forgetting (Hardt et al., 2013). It has been argued that memories that are based on experiential episodes are less susceptible to interference than those based on familiarity (Sadeh et al., 2014). Whether clustering relates to the stability of memory and to forgetting, however, has not been investigated before. Previous studies have only indexed spatial clustering in immediate or shortly delayed tests, i.e., in the order of minutes (Miller et al., 2013a,b). In those setups, consistent correlations of clustering and recall performance have been found. Yet, the persistence of these associations over extended periods remains unknown.

A second important issue is related to the role of active behavior in the segmentation of long-term memory and its relationship with the clustering phenomenon. In general, spatial clustering effects have been interpreted as the consequence of the association of items with a gradually changing internal representation of context (Polyn et al., 2009). It has been argued that this continuously shifting context representation is modified more abruptly at the encounter of spatial frontiers (Horner et al., 2016). Studies have shown the role of spatial limits in weakening the long-term links between information preceding and following the boundaries, organizing long-term memory into discrete episodes (Ezzyat and Davachi, 2011). Critically, theories have proposed that in addition to spatial factors, action-related variables play a key role in defining event boundaries. In particular, Event Segmentation Theory (Zacks et al., 2007) suggests that an agent's processing of bottom-up and top-down inputs (e.g., sensory information related to its own movements or internal goals) are fundamental in the definition of the limits of working memory.

Although the role of active learning in the modulation of memory struc-

ture has not been investigated before, several studies have explored how self-directed learning affects mnemonic performance. One of the primary variables influencing spatial memory has been theorized to be volition during navigation, or the possibility to intentionally decide on the routes to take (Chrastil and Warren, 2012; Grant and Magee, 1998; Betella et al., 2013). Studies have shown that active learning benefits memory in visual recognition tasks (Kornell and Metcalfe, 2006; Voss et al., 2011a,b), suggesting a relevant role of agency in the organization of acquired knowledge. Moreover, the physiology of the hippocampal-entorhinal system points to a fundamental role of action-related signals during memory formation (Rennó-Costa et al., 2010).

We designed two experiments to evaluate the persistence of spatial clustering effects over time and the role of active navigation in free recall dynamics. In experiment 1, we aimed to replicate the spatial clustering results reported by Miller et al. (2013b), and to test their persistence 24 hours after learning. We hypothesized to find significant spatial clustering effects in both the immediate and delayed tests. In experiment 2, we followed a mixed design to evaluate the joint influence of navigation type and time elapsed from encoding. Given the positive influence of volition on spatial learning and the modulation of memory formation by action previously discussed, we hypothesized to find increased clustering in the active navigation condition as compared to the passive one.

4.2 Experiment 1

4.2.1 Methods

Participants

Participants were 22 young adults (14 males, age 28.72 ± 6.9 years) recruited from Universitat Pompeu Fabra’s student community. To estimate the sample size, we took as reference experiment number 2 of Miller et al. (2013a), in which 14 participants were tested. Given that our setup included an ad-

ditional spatial clustering test (24 hours delayed), we increased this N size in order to reach a total number to 22 subjects. All participants provided informed consent to participate in the experiments, which was approved by the local Ethical Committee “Clinical Research Ethical Committee (CEIC) Parc de Salut Mar” (Barcelona, Spain).

Procedure

We asked our participants to explore a Virtual Environment (VE) to find and memorize 13 3D objects presented at specific locations. The VE included buildings, houses, and streets, representing an old town. Objects had not specific thematic links with any location in the environment, but to avoid possible associations between models and space, we predefined locations of presentation and randomly assigned the items to these sites for each subject independently. The task at each trial consisted of approaching a particular target object indicated on the screen in written text (e.g., “Please find the trash bin”, Figure 4.1A, Top). Once subjects had reached the correspondent object, instructions were updated with a new item to find and approach. Participants were instructed to visit all objects and memorize them; they were not required to remember the layout of the town or the positions of the objects. After the thirteenth item was visited, the screen turned grey and the message “***” indicated the start of a free recall session (immediate, T1). Ninety seconds were given to verbally recall as many items as possible in any order, while responses were audio-recorded. Twenty-four hours later (T2), a second “surprise” free recall test was conducted (i.e., subjects were not informed about this test during the first session), lasting for 90 seconds again. At T1, the assessment was conducted in the laboratory and at T2 participants were reached via a telephone call. The sequence of objects to visit was randomized. The starting position in the town was randomly determined from four predefined locations covering the main quadrants. A timeline of the experiment can be seen in Figure 4.1B, Top. Three-dimensional objects were built with equivalent levels of details and textures using Autodesk Maya (San Rafael, CA, Figure 4.1C).

The VE was implemented with the Unity3D game engine (San Francisco, CA). Participants were allowed to control navigation with a joystick or with the keyboard and the mouse depending on their preference. Concerning numbers of items to be remembered, recall times, encoding modality, and overall instructions given to the participants, our experimental protocol had no differences with that of Miller et al. (2013b), except that we used objects instead of stores and introduced the surprise test 24 hours after the navigation session. On average, participants took 7.6 ± 3.2 minutes to visit all items before starting the retrieval phase of the experiment. Two example trajectories of two different trials of the same subject can be seen in Figure 4.1D.

Dependent Variables

We measured recall performance and recall dynamics at T1 and T2. The recall performance score (from 0 to 1) was obtained by normalizing the number of items correctly retrieved by the total number of stimuli (13 in this experiment). Items repeated and intrusions of extra-list items were excluded from the analysis.

To quantify the level of spatial structuring of objects at recall, we used the spatial clustering score (SCs), a measure of the tendency to consecutively retrieve items encountered in more proximate spatial locations (Miller et al., 2013b,a). For each trial, every transition between a recollected item and the following was ranked based on their spatial location. If the distance was the shortest of all possible, the transition was given a score of 1. If it was the longest, it was given a score of 0. For each subject, an average score was calculated. We defined a measure of global Spatial Clustering scores gSCs as the average of the SCs obtained at T1 and T2.

To compare the spatial versus temporal organization of participant's responses, we also calculated a temporal clustering score (TCs, Polyn et al., 2009). We assigned to each recall transition a ranked score reflecting the serial order proximity of the two items during navigation. We averaged those values, resulting in a single TCs per subject.

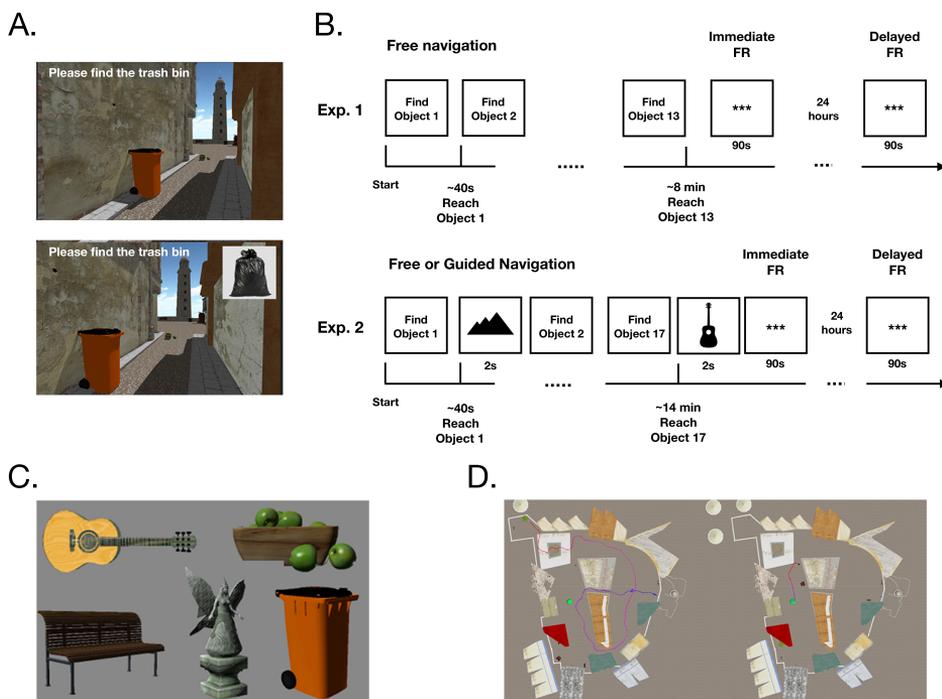


Figure 4.1: Task description. A) Stimulus presentation during the navigation phase of experiment 1 (top), and 2 (bottom). Participants are instructed to find a specific object, in this case, the trash bin. In experiment 2, after reaching the model, an image is presented on the screen for 2 seconds. B) Timeline of experiment 1 (top), and 2 (bottom). C) Example objects that were used as stimuli to memorize (experiment 1) or to indicate locations in the environment (experiment 2). D) Top view of the environment showing the trajectory of 1 participant in two different trials.

We quantified the number of items only reported at T1 (i.e., forgotten), those repeated in both immediate and delayed tests and those reported only at T2 (recovered). We calculated a measure of overlap by dividing the number of items reported at T1 and T2 by the total number of items reported in both experiments for each participant separately. Note that this measure is independent of overall performance, for instance subject 3 had an overlap score of 1 in experiment 1 but his global performance was of 0.69 (Supplementary Figure 4.4A).

4.2.2 Results

Significant SCs in immediate free recall

We first aimed to replicate the spatial clustering effects reported in the literature. We quantified clustering at T1 by calculating a mean SCs for each participant. To assess the significance of the observed values with respect to chance, we employed methods used previously (Miller et al., 2013b,a). Theoretically, chance level in the spatial clustering comparison is expected at 0.5. However, to more accurately estimate the significance of the SCs in our particular dataset, and obtain a more reliable estimate of the baseline SCs of each subject, we used a bootstrapping procedure. For each subject independently, we calculated the SCs using a permutation test with 1000 iterations, in which the order of the recalled items on each trial was randomly permuted. By using the same items that were recalled, this procedure allowed us to build a null hypothesis distribution free of any assumptions on the statistical properties of the data. Instead of using the Student's t distribution to compare the observed SCs against chance, we compared the observed distribution of SCs across subjects with the generated null hypothesis distribution. We found a significant difference between the two sets of values at T1, $t_{(21)} = 3.8$, $p < 0.01$, $d = 0.81$, indicating that the structure with which participants organized items in memory was indeed spatial in the immediate test.

Figure 4.2A left shows this effect: the conditional response probability (CRP) of recalling two consecutive items is plotted as a function of spatial distance, binned into thirds. We estimated the likelihood of successively recalling an object of a given spatial bin by dividing the frequency of actual transitions by the frequency of all possible transitions for each subject separately (Miller et al., 2013a). We observed a tendency of CRPs to decrease as distance increases between recalled values.

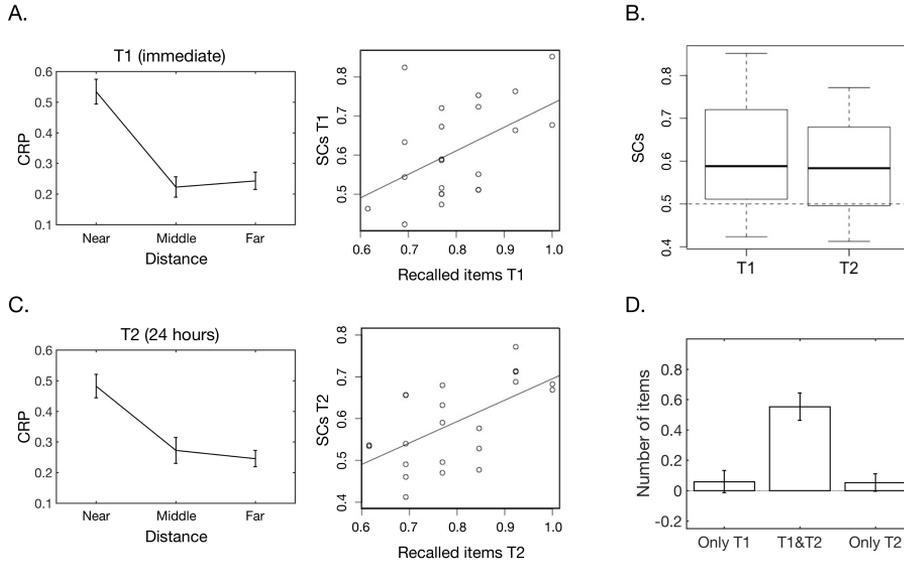


Figure 4.2: Results from experiment 1. A) Left: CRP as a function of spatial distance at T1. Right: SCs and recall performance (normalized) in the immediate test. B) SCs at T1 and T2 are not significantly different, but significantly higher than chance in both the immediate and 24 hours delayed tests. Dotted line indicates chance level. C) Left: CRP as a function of distance at T2. Right: SCs and recall performance (normalized) in the delayed test. D) Number of items recalled only at T1, at T1 and T2, and only at T2. Error bars in A, C, and D indicate standard error of the mean (SEM). Black line in A and C (right) shows the least square fit.

Correlation of SCs and memory performance

Previous literature has shown positive correlations of clustering scores and mnemonic performance (Sederberg et al., 2010). In general, it has been reported that participants who exhibit stronger temporal and spatial continuity effects also tend to recall more items. We therefore assessed the correlation between SCs and recall performance in the immediate test. Both clustering and recall scores at T1 were normally distributed (Shapiro Wilk, $p > .05$). We used Pearson's correlation coefficient to quantify the statistical dependence of the two variables. We found a significant positive correlation in the immediate test $r_{(20)} = 0.48$, $p < .02$, Figure 4.2A, right.

SCs are maintained and correlate with performance in delayed free recall

We next aimed to assess the persistence of spatial clustering effects over time and their correlation with recall performance after the 24 hours' interval. We first compared SCs to chance in the delayed test using the same permutation procedure as in T1. This time, we shuffled the order of the items reported at T2 while preserving the same items. Results indicated that SCs were, again, significantly higher than chance $t_{(21)} = 2.93$, $p < .01$, $d = 0.62$. The CRPs as a function of spatial distance is plotted in Figure 4.2C, left. No significant differences between clustering scores at T1 and T2 were observed $t_{(21)} = 0.78$, $p = .43$, $d = 0.17$, Figure 4.2B. Both the SCs and recall scores at T2 were normally distributed (Shapiro Wilk, $p > .05$). Pearson's correlation coefficient indicated that, as in the immediate test, the two variables were positively correlated, $r_{(20)} = 0.59$, $p < .01$, Figure 4.2C, right.

Recalled items at T1 and T2 largely overlap

Recall performance at T1 and T2 were not significantly different $t_{(21)} = 0.26$, $p = .79$, $d = 0.05$; two-tailed, paired t -test. The average overlap score across participants was $.83 \pm .01$ while a small percentage of items were forgotten: $.09 \pm .1$, or reported only at T2: $.08 \pm .08$ (Figure 4.2D, see Supplementary Figure 4.4A for the individual data).

We found a significant correlation of gSCs — the mean of T1 and T2 SCs —, and overlap scores $r_{(20)} = 0.55$, $p < .001$. The correlations of gSCs with forgetting and recovery scores were non-significant (forgetting: $r_{(20)} = -.24$, $p = .26$; recovery: $r_{(20)} = .05$, $p = .81$, Supplementary Figure 4.7).

Temporal factors at T1 and T2

Previous setups have reported simultaneous temporal and spatial clustering during virtual navigation (Miller et al., 2013a). We therefore assessed whether our participants clustered their responses according to the serial order of presentation of objects during the encoding phase of the experiment.

We did not observe a temporal *contiguity* effect at T1 or T2, T1: $t_{(21)} = 1.45$, $p = 1.59$; T2: $t_{(21)} = .39$, $p = .7$, t -test against chance (Supplementary Figure S2A). We did observe a tendency to recall items in forward order, especially at T1 (black circles curve). We also observed an increased likelihood of recall for items encountered in serial positions close to the end of the study list, a *recency* effect more pronounced in the immediate test (Figure 4.5A, right). Although TCs were not significantly different from what is expected by chance, we observed a significant negative correlation between TCs and recall performance in the immediate test, $r_{(20)} = -.46$, $p < .03$, Figure 4.6A, left. This effect was not observed, however, at T2, $r_{(20)} = -.03$, $p = 0.9$, Figure 4.6A, right.

No interaction of SCs and TCs

The randomization we applied to the localization of the objects and sequences of visits prevents for possible confounds between spatial and temporal clustering. Nevertheless, we sought to control for any possible interaction between the two variables in our analyses. For each subject independently, we calculated a correlation value between spatial and temporal clustering scores from all transitions (a SCs and TCs for each pair of consecutively recalled values). This allowed us to assess whether reported transitions in which spatial clustering was high also showed increased temporal clustering, and those in which spatial factors were low showed also decreases in TCs.

In the immediate test, only 1 of the 22 participants showed a significant negative correlation between the 2 variables (Subject 21, see Supplementary Table 5.1 for the individual data). At the group level, r values were not significantly different from zero, $t_{(21)} = .36$, $p = 0.71$. In the delayed test, one participant of 22 showed a significant positive correlation (Subject 2, Supplementary Table 5.1 for the individual data), and at the group level, again, correlations were not statistically higher than chance, $t_{(21)} = 1.25$, $p = .22$.

4.3 Experiment 2

Results from experiment 1 showed that our VR based navigation task could capture the dynamics of spatial clustering previously observed in the literature. Moreover, they revealed a long-lasting effect that could be identified 24 hours after learning. In experiment 2, we aimed to evaluate the joint contribution of navigation types and time elapsed after learning in SCs and performance.

4.3.1 Methods

Participants

Participants were 28 young adults (17 males, 25.6 ± 5.4 years) recruited from Universitat Pompeu Fabra’s community. We increased the number of subjects with respect to experiment 1 in order to account for the differences in the experimental design, which included a within and a between groups comparisons. All participants provided informed consent to participate in the experiment, which was approved by the local Ethical Committee “Clinical Research Ethical Committee (CEIC) Parc de Salut Mar” (Barcelona, Spain).

Procedure

The overall procedure was the same as in experiment 1 with three exceptions. First, since we observed a ceiling effect in the recall scores of three participants in experiment 1 (one subject at T1 and two at T2), we increased the total number of objects in experiment 2 — 17. Second, to control for differences in exposure time to items — a possible confounding factor in experiment 1, in which objects were visible during the whole navigation block —, we associated a specific image to each of the 3D objects and instructed the participants to remember the images instead of the objects. Images were presented on the screen only when subjects reached the target item at each trial and remained visible for 2 seconds (Figure 4.1A, bottom). As in Miller et al. (2013a), images were semantically linked to the 3D objects

(e.g., a trash bag to a trash bin, 4.1A, bottom). Third, participants were divided into two groups (G1, G2) that differed in the degree of control over navigation. In G1, subjects controlled navigation as in experiment 1. In G2 they were passively exposed to the trajectory of a participant from G1. We conducted two free recall tests after the learning phase (immediate, T1, 24 hours delayed, T2). Mean duration of navigation in the active condition was 14.3 ± 5.52 . A timeline of the experiment is presented in Figure 1B, bottom.

4.3.2 Results

Significant SCs in immediate and delayed free recall

Before assessing the joint contribution of navigation types and time elapsed after learning in the SCs, we checked whether such scores were significant at T1. In both G1 and G2 SCs were higher than the mean of the generated null hypothesis distribution, G1: $t_{(13)} = 2.75$, $p = .02$; G2: $t_{(13)} = 3.88$, $p < .01$, permutation procedure, Figure 4.3A. We built a mixed ANOVA model with between factor navigation type and within factor measurement time to estimate the relationship with SCs. Results revealed that the SCs in G1 and G2 were not significantly different (no main effect of navigation type: $F_{(1,26)} = 2.72$, $p = .11$, $\eta^2 = .25$, Figure 4.3A). To increase statistical power, we aggregated data from both groups in the subsequent analyses.

We tested whether the significant SCs observed in the immediate test were maintained in the 24 hours' assessment. Again, SCs were significantly different from the distribution built from participants' T2 responses, $t_{(27)} = 1.45$, $p < .01$. SCs at T1 and T2 did not significantly differ, $F_{(1,26)} = .79$, $p = .38$, $\eta^2 = .35$. No interaction between navigation type and time of testing was found $F_{(1,26)} = .19$, $p = .66$. The CRP curves as a function of spatial distance are presented in Figure 4.3B (T1, left; T2, right).

Memory performance was not affected by active versus passive learning or by the time of learning. There was not main effect of study time on the number of items recalled $F_{(1,26)} = .19$, $p = .64$, $\eta^2 = .007$, nor a main effect

of navigation condition $F_{(1,26)} = .18$, $p = .67$, $\eta^2 = .006$. No interaction between the two variables was found $F_{(1,26)} = .18$, $p = .67$, $\eta^2 = .007$.

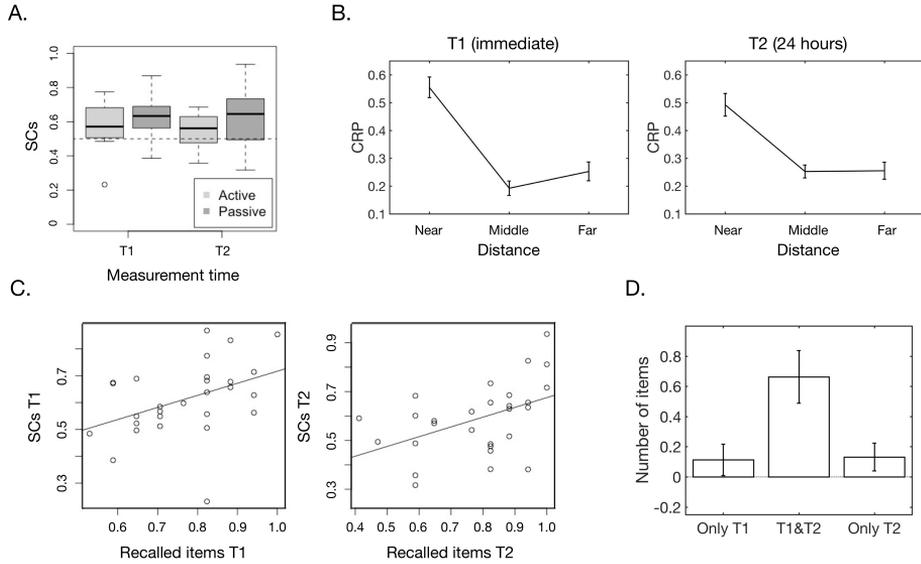


Figure 4.3: Results from experiment 2. A) SCs for active and passive, T1 and T2 conditions. Dotted line indicates chance. B) CRP as a function of distance at T1 (left) and T2 (right). C) Correlation of SCs and recall performance in the immediate (left) and delayed (right) tests. Black line shows the least squares fit. D) Number of items recalled only at T1, at T1 and T2, and only at T2. Error bars in panels B and D indicate \pm standard error of the mean (SEM).

Clustering and recall scores are correlated in immediate and delayed free recall

We assessed the degree of correlation between SCs and recall performance at T1 and T2. Shapiro Wilk's test revealed that both recall and clustering scores were normally distributed ($p > .05$ in all comparisons). Pearson's correlation coefficient showed a significant correlation between the two variables in both the immediate and delayed tests, T1: $r_{(26)} = .41$, $p = .03$, Figure 4.3C, left; T2: $r_{(26)} = .45$, $p = .01$, Figure 4.3C, right.

gSCs and forgetting scores are negatively correlated

Recall performance was not significantly different between T1 and T2, $t_{(27)} = .44$, $p = .65$. We quantified an overlap of responses of $.73 \pm .17$ in both tests. Items only reported at T1 but not T2 (i.e., forgotten) were $1.32 \pm .13$ items, and $1.34 \pm .10$ were reported at T2 but not T1 (recovered, Figure 4.3D, see Supplementary Figure 4.4B for the individual data).

As in experiment 1, gSCs significantly correlated with overlap scores $r_{(20)} = 0.54$, $p < .001$. We also found a significantly negative correlation of gSCs and forgetting, $r_{(20)} = -.47$, $p < .001$. We did not find a relationship between gSCs and recovery scores: $r_{(20)} = -.29$, $p = .13$, Supplementary Figure 4.7.

Significant temporal clustering at T1 and T2

Contrary to experiment 1, participants significantly clustered their responses according to the order of presentation of items during navigation in the immediate test, $t_{(27)} = .3.73$, $p < .01$. In the delayed assessment, they still showed a significant serial order effect, $t_{(27)} = 2.3$, $p = 0.03$, t -test against chance in both comparisons. The lag-CRP in Supplementary Figure 4.5B, left shows the increased probability to consecutively recall items presented in consecutive serial order during navigation. There were no recency effects in this experiment (Supplementary Figure 4.5B, right).

To assess whether the differences in TCs between experiments were related to the active and passive conditions we built a second mixed ANOVA model to estimate the relationship of TCs, navigation types and measurement times. Results revealed a lack of significant main effects both for navigation, $F_{(1,26)} = 0.07$, $p = .79$, $\eta^2 = .002$, and measurement time, $F_{(1,26)} = 2.84$, $p = .10$, $\eta^2 = .09$, and a non-significant interaction between the two variables, $F_{(1,26)} = 1.12$, $p = .29$, $\eta^2 = .04$.

We evaluated the correlation between TCs and recall performance at T1 and T2. We observed a tendency for participants who clustered their responses in the temporal dimension to also perform better in the memory test at T1, $r_{(26)} = .32$, $p = .09$, Figure 4.6B, left. A significant correlation of TCs and

recall performance was also found at T2, $r_{(26)} = .38$, $p = .04$, Figure 4.6B, right.

Given the significant spatial and temporal clustering scores observed in both the immediate and delayed tests and the significant correlation observed at T2, we checked whether SCs and TCs correlated at the trial (i.e. transition) level. Our analysis revealed that none of the participants at T1 showed a significant correlation between SC and TC scores, and only one subject at T2. At the group level, correlations were not significantly different from zero in any of the two tests, indicating that these two variables did not interact, T1: $t_{(27)} = 1.49$, $p = .14$; T2: $t_{(27)} = 1.92$, $p = .06$.

4.4 Discussion

We have investigated recollection dynamics in immediate and 24 hours delayed free recall of items studied under active and passive navigation conditions. By integrating methods from the study of memory and spatial behavior, we were able to extend previously reported spatial clustering effects and assess their modulation by navigation types and their persistence over a 24 hours' delay period. We present four main findings that were consistent across our two experiments (unless specified). First, significant SCs were found in the immediate and delayed tests, which were unaffected by navigation types in experiment 2. Second, SCs and recall performance were positively correlated both in the immediate and the delayed tests. Third, global SCs positively correlated with overlap scores across experiments and negatively correlated with forgetting in experiment 2. Fourth, the influence of spatial and temporal clustering on recall performance was independent in both the immediate and the delayed assessments.

Our first results replicate previous studies demonstrating a spatial structure in the recall of items learned during navigation. In accordance with those studies, our results reveal that this structure was significantly different from that of a randomly generated distribution constructed by shuffling the order in which the items were recalled. The effect was significant in the immedi-

ate test across experiments, and with a large effect size (Experiment 1: $p < .001$, $d = 0.81$, Experiment 2: $p < .001$, $d = 0.89$, data aggregated from G1 and G2). Importantly, we also found significant SCs in the delayed tests and no differences in clustering scores across time points. These results provide, to our knowledge, the first evidence for the persistence of the spatial structuring of items for a period extending hours after learning. Previous studies have reported increased SCs in final free recall as compared to immediate tests (Klein et al., 2005). Temporal clustering has also been observed on time-scales on the order of minutes in delayed free recall (Howard and Kahana, 1999; Miller et al., 2013a). Investigations have pointed to an increase in semantic clustering after sleep (Takeuchi et al., 2014). Our results did not reveal higher clustering scores in the 24 hours' test but point to a stabilization of SCs in that period, indicating a role in long-term memory. In future research, we aim to assess the evolution of clustering at different time delays, including shorter and extended periods of time to further evaluate this idea.

On the other hand, the null effect we observed in the navigation type comparison was unexpected. Indeed, prominent theories of human learning attribute a high relevance to an individual control over the learning process, and the benefits of self-directed learning specifically in memory are well acknowledged (Kornell and Metcalfe, 2006; Gureckis and Markant, 2012; Voss et al., 2011a,b). In traditional “active learning” paradigms, however, the active condition typically includes the possibility to control items of study, times of exposure and intervals. Equivalent learning conditions were met in our first experiment but only partially in the second, in which the stimulus presentation time was fixed. Whether SCs are affected when materials and timings of study are in control of the learner will remain to be determined in future research. A second important issue to further explore relates to the role of active physical movement as opposed to stationary visualization in the segmentation of events and the clustering effect. Indeed, studies in the human navigation literature have shown that proprioceptive / vestibular information associated with movement is a strong determinant of spatial

learning, while null effects have been typically reported in studies comparing active versus passive navigation conditions in desktop VR (Chrastil, 2013; Chrastil and Warren, 2012; Taube et al., 2013). Moreover, in the light of theories of event segmentation (Zacks et al., 2007), the processing of sensory information related to movement could influence the segmentation of working memory, chunking experiences for long-term storage.

Our second result — the correlation of recall and clustering scores in the immediate and delayed tests — is consistent with several studies that have reported positive associations of recall performance and clustering in the temporal, semantic and spatial dimensions (Polyn et al., 2009; Kahana, 2012). In previous work, however, correlations have only been shown in immediate tests. We replicate and extend those findings, providing evidence for a long-lasting statistical dependence of SCs and recall performance. Our results in the delayed test are particularly relevant considering current theories of forgetting, which posits that it is the nature of memory, i.e., whether it is based on recollection or familiarity, that determines the rate and form of the process (Sadeh et al., 2014). Indeed, it has been proposed that source memories are less susceptible to interference than item memories, but more to decay. In our paradigm, participants did not explicitly reported remember-know judgements and therefore SCs cannot be directly linked to either of the two types of memories (Mickes et al., 2013). Indeed, familiarity-based memories could have high SCs if spatially structured, and low clustered items could be reported as the result of a recollection process. Whether SCs correlate with recollection / familiarity judgements is currently unknown and a relevant issue to further research. A second important issue to investigate in the future relates to whether spatial clustering is more vulnerable to decay or interference.

Despite these unknowns, our third main result revealed that SCs correlated with the degree of overlap in the items that are remembered after the 24 hours' delay. This indicates that participants who clustered more their items in the spatial dimension also tended to recall the same items at the two moments in time. Moreover, data from experiment 2 demonstrated that

high SCs were associated with a decrease in forgetting in the 24 hours' interval, a tendency which was not observed, however, in experiment 1.

It must be noticed that our overlap analyses revealed that the majority of items remembered at the immediate test were the ones remembered at T2. Additional analysis in which temporal clustering at T2 was assessed by taking as a reference the order of recollection at T1 (rather than serial order of presentation of items during learning) showed that recall sequences were similar at both time points ($p < .01$ in both experiments). This suggests that the clustering effects observed in the T2 test were influenced by initial retrieval (see also (Miller et al., 2013a). Since our primary objective in this setup was to assess the stability of SCs over time, our experimental design included two free recall tests, separated by a delay, and performed on the same subjects. This methodology allowed us to quantify the relation of SCs at T2 and overlapping and forgotten items. In the light of our results, however, it would be relevant to investigate in the future the magnitude of remote spatial clustering in a condition with no initial test (i.e., free of the output encoding effects of the T1 assessment).

Finally, our fourth result — the lack of interaction between temporal and spatial clustering in all four free recall tests — is consistent with previous literature which has shown independent modulations of recall performance by these two factors (Miller et al., 2013a). Note that TCs were quite different across our two experiments. While in the first setup we did not observe significant serial order effects in the immediate or delayed tests, in experiment 2 they were significant at both time points. A simple interpretation of these results would suggest that the active-passive distinction played a role in the TCs, however, analyses revealed no differences between TCs across G1 and G2 nor an interaction between navigation type and measurement time with regard to the temporal clustering factor. It is possible that the lack of significant temporal clustering effects in experiment 1 was due to the presence of the objects in the environment during the whole navigation period, implying multiple visualizations of the stimuli, and thus a more complex sequence of exposures to the material. Although TCs were not

significantly different than chance at our two measurement times in experiment 1, we found a negative correlation with recall performance at T1 and a non-significant correlation at T2. In experiment 2, positive correlations between the two variables were found at the two time points. Despite these different patterns of TCs likely reflecting differences in our experimental protocols, across four assessments the interactions between TCs and SCs were not higher than what would be expected by chance, pointing to an additive rather than combined influence in overall recall.

The study of recollection dynamics in free recall has been instrumental in characterizing the organizational structure of human memory (Kahana, 2012). Our results suggest that, when information is encoded spatially, the distance between items is a long-lasting determinant of such structure. This knowledge could be useful in the design of novel human-data interaction paradigms capitalizing on technologies for data spatialization (Pacheco et al., 2014).

4.5 Supplementary Information and Figures

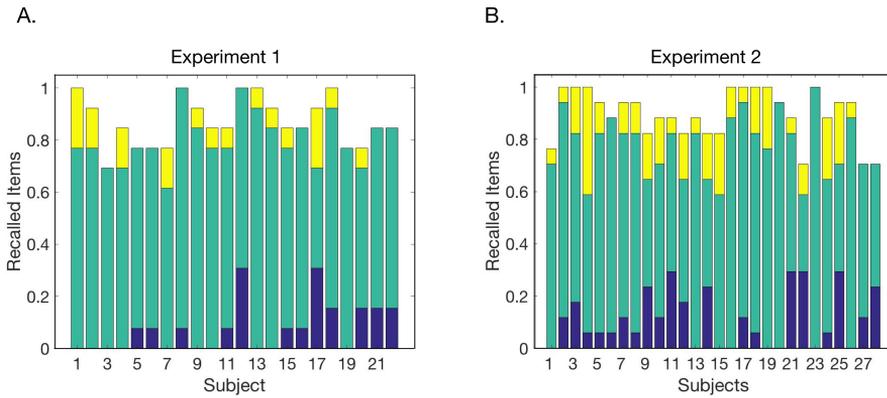


Figure 4.4: Overlap of responses at T1 and T2. Stacked bars show number of items recalled only at T1 (blue), at T1&T2 (green), and only at T2 (yellow). Bar height indicates for each subject, the total number of items recalled across time points (normalized). A) Data from experiment 1. B) Data from experiment 2.

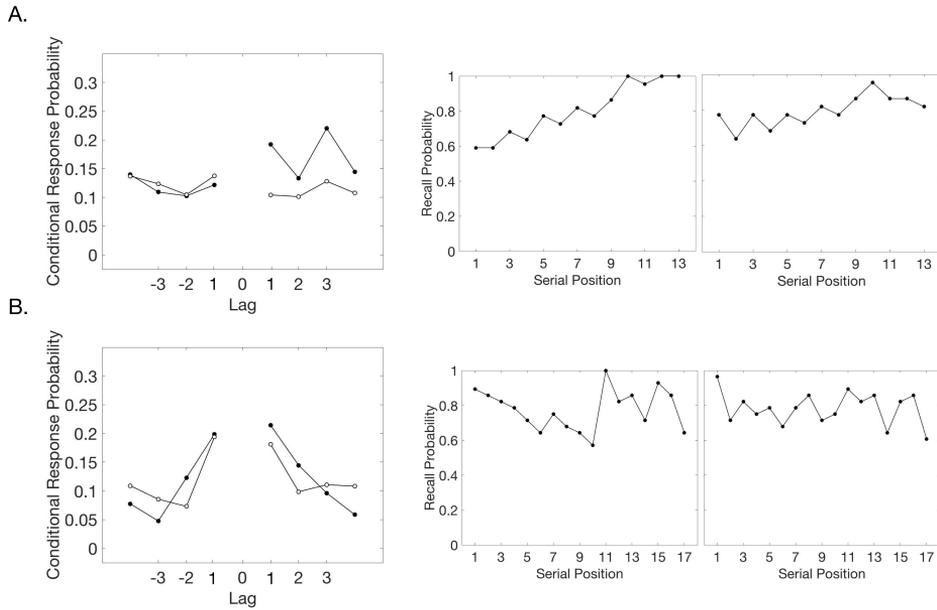


Figure 4.5: Lag-CRP and recency effects. A) Left: CRP as a function of order of presentation of items during the learning phase of experiment 1 at T1 (black circles) and T2 (white circles). The curve shows the probability of recalling an item from serial position $i+\text{lag}$ after recalling item from serial position i . No strong contiguity effects were observed in the immediate or delayed tests. Right: Serial position curve for T1 (left) and T2 (right) in experiment 1, showing the likelihood of recalling an item as a function of its serial order of presentation during navigation. B) Left: CRP as a function of order of presentation of items during the learning phase of experiment 2 at T1 (black circles) and T2 (white circles). Contiguity effects typically observed in free recall can be seen in the increased probability of consecutively recalling temporally closer items in forward and reverse order. Right: Serial position curve for T1 (left) and T2 (right).

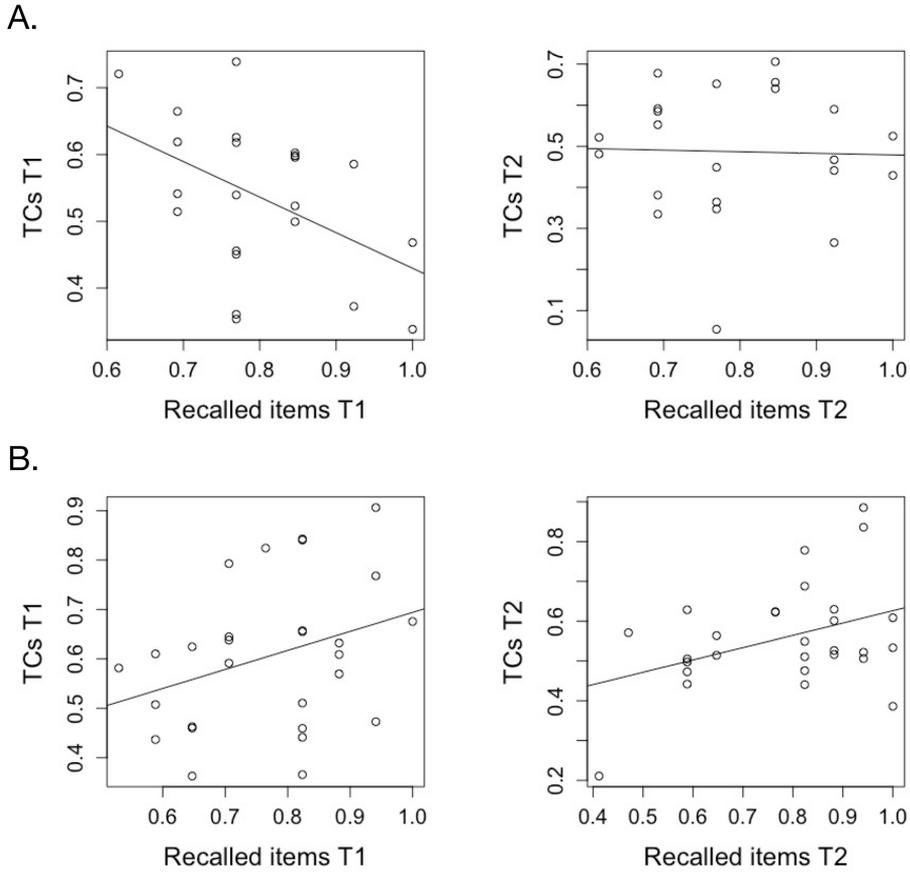


Figure 4.6: Temporal Clustering and Recall Performance. A) TCs as a function of recall performance in experiment 1 a T1 (left) and T2 (right). A significant negative correlation was found at T1 but not at T2. B) TCs as a function of recall performance in experiment 2 a T1 (left) and T2 (right). A significant correlation was found at T1, and a tendency ($p = .09$) at T2. Black line in all plots indicates least square fit.

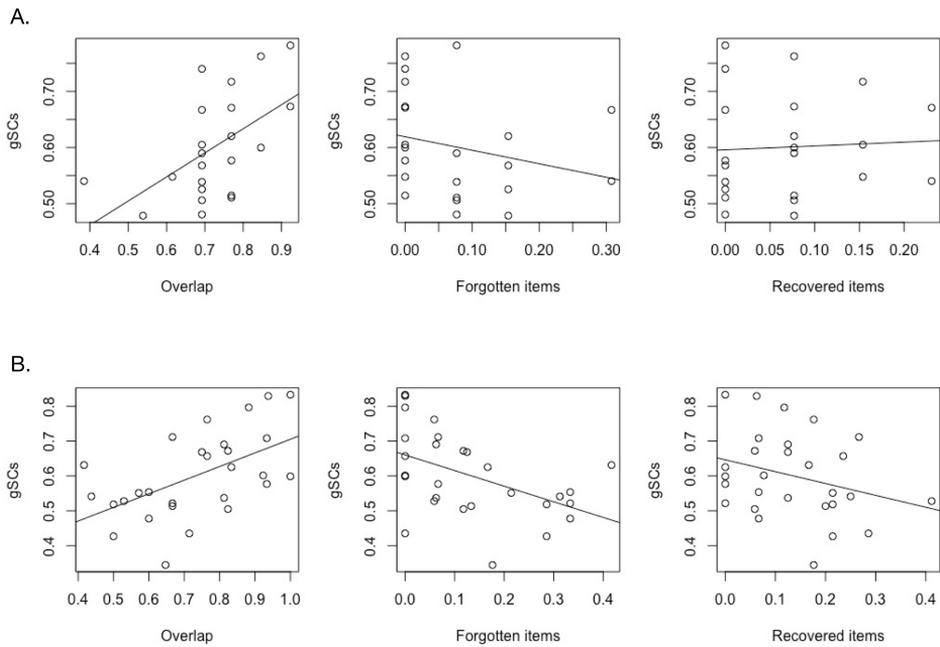


Figure 4.7: Global SCs (gSCs) vs. overlap, forgotten and recovered items. A) Experiment 1. Left: gSCs as function of item overlap across T1 and T2. Middle: gSCs as a function of forgotten items (i.e., only reported at T1). Right: gSCs as a function of recovered items (i.e., only reported at T2). B) Experiment 2. Left: gSCs as function of item overlap. Middle: gSCs and forgotten items. Right: gSCs and recovered items.

Table 4.1: SCs and TCs correlation in experiment 1

Subj	T1		T2	
	r	p	r	p
1	-0,25	0,52	-0,62	0,03
2	-0,51	0,16	0,24	0,47
3	-0,18	0,67	0,68	0,06
4	0,32	0,44	0,17	0,64
5	0,22	0,57	-0,29	0,48
6	0,08	0,85	0,67	0,07
7	-0,19	0,68	0,24	0,54
8	0,19	0,58	-0,18	0,6
9	0,16	0,67	0,05	0,89
10	0,45	0,22	-0,14	0,71
11	-0,64	0,07	-0,49	0,18
12	0,19	0,57	-0,48	0,23
13	-0,32	0,33	-0,03	0,93
14	0,42	0,22	0,27	0,42
15	0,25	0,52	0,38	0,31
16	-0,06	0,87	0,31	0,42
17	-0,01	0,98	0,44	0,32
18	0,34	0,31	-0,01	0,98
19	-0,36	0,34	-0,2	0,6
20	0,31	0,45	0,65	0,11
21	-0,82	0,01	0,21	0,62
22	-0,2	0,57	0,33	0,43

Table shows the Pearson correlation coefficient r and correspondent p -values between SCs and TCs extracted from each transition of recollected items, separately for each participant of the experiment, at T1 and T2.

Table 4.2: SCs and TCs correlation in experiment 2.

Subj	T1		T2	
	r	p	r	p
1	0.29	0.39	-0.48	0,11
2	-0.39	0.15	-0.34	0,23
3	0.29	0.33	-0.16	0,6
4	-0.24	0.54	0.14	0,61
5	-0.21	0.49	-0.42	0,13
6	0.01	0.97	0.01	0,99
7	-0.30	0.30	-0.34	0,25
8	-0.02	0.93	0.06	0,82
9	-0.15	0.68	-0.51	0,16
10	-0.45	0.16	-0.20	0,53
11	0.01	0.98	0.23	0,54
12	0.09	0.79	-0.14	0,7
13	-0.14	0.64	0.11	0,7
14	0.07	0.84	0.74	0,02
15	-0.01	0.97	-0.33	0,26
16	0.28	0.34	-0.37	0,17
17	-0.35	0.20	0.18	0,54
18	-0.24	0.42	-0.48	0,07
19	0.01	0.96	-0.31	0,25
20	0.02	0.94	-0.44	0,1
21	-0.33	0.26	-0.61	0,08
22	0.15	0.70	0.73	0,1
23	-0.47	0.08	-0.45	0,09
24	-0.24	0.50	-0.39	0,18
25	-0.20	0.54	0.07	0,85
26	0.10	0.72	0.22	0,42
27	0.44	0.17	0.23	0,54
28	0.09	0.78	0.22	0,63

Table shows the Pearson correlation coefficient r and correspondent p -values between SCs and TCs extracted from each transition of recollected items, separately for each participant of the experiment, at T1 and T2.

Theta oscillations in the human hippocampus during active learning

In the second experiment of Chapter 4, we compared memory for items studied actively and passively, and reported non-significant differences in performance between the two conditions. We argued the null results observed might be due to the operationalization of active learning in that setup, and suggested the need of studying the quality of memory when timings and materials of study are in control of the learner.

In this section, we addressed this problem in a behavioral (N=23) and a neurophysiological (N=6) study. We compared recognition memory for items learned in a condition in which participants actively determined what stimulus to study and for how long, versus a condition with no control over the flow of learning. The text presented in this section is part of a manuscript in preparation entitled “Theta oscillations in the hippocampus during

active learning”, which will be submitted to a specialized journal on the neurophysiology of memory during 2018. The abstract reads:

The benefits of self-directed learning on memory are well-acknowledged. Several studies have reported increases in memory performance when timings and materials of study are in control of the learner as opposed to a passive exposure to information. We know very little, however, on the neural correlates of active learning in humans. Recent fMRI studies have shown a critical role of the hippocampus in the process, as observed in its increased BOLD activity for active (i.e., self-directed) knowledge acquisition as compared to passive exposure to information. Due to the limited time-frequency resolution of fMRI, however, the specific oscillatory signatures of volitional learning in the hippocampus are not known. Here, we used intracranial EEG (iEEG) recordings from human epilepsy patients to investigate hippocampal oscillations during self-directed learning. We designed a Virtual Reality (VR) memory test in which participants navigated a square virtual environment and memorized discrete images presented at specific locations. Critically, subjects could control navigation and information intake in one condition (volitional) but were passively transported along the trajectory previously chosen by another participant in a second condition (passive). We tested the participant’s memory for the learned items using a classic recognition memory test in which subjects reported their old/new responses in a 6 point confidence scale. In addition to our group of patients ($N=6$), we conducted the test with twenty-three healthy subjects as a control. Behavioral results from our control experiment revealed prominent differences in recognition accuracy across active and passive navigation modes. Participants recognized items in the active condition significantly better, and had higher levels of confidence in

their responses. Moreover, results from our iEEG study confirmed important differences in the patterns of hippocampal oscillatory power across conditions. The active learning condition was associated with increased theta (2-7z) oscillations in that brain structure as compared to the passive one. Our results are consistent with the increases in hippocampal theta oscillations seen in the rodent during active information sampling, demonstrating for the first time a link between volitional learning and hippocampal theta power in humans.

5.1 Introduction

The distinction between active and passive learning has been a highly influential topic of investigation across different research fields. For instance, in the learning sciences, a widely advocated argument is that people learn better when the materials and timings of study are under their control (Council et al., 1999; Sylva et al., 1976; Montessori, 2013). Similar ideas are prominent in theories of human perception and action, which have emphasized the relevance of deciding what information to study on a moment by moment basis for better learning (Gibson, 2014; Piaget, 1953)

Although at a behavioral level, the empirical evidence supports the notion that controlling the flow of information intake during learning enhances subsequent performance in memory tests (Gureckis and Markant, 2012; Kornell and Metcalfe, 2006), few studies have looked at the neural correlates of active learning in humans. Two recent fMRI studies have addressed this issue, showing greater engagement of the hippocampus during volitional as compared to passive learning in a spatial 2D memory recognition task (Voss et al., 2011a,b). Due to the limitations of fMRI, however, the particular time-frequency characteristics of active learning in the hippocampus remain unknown.

In the rodent literature, a brain rhythm that has been associated with active behavior is hippocampal theta (4-8Hz). Theta has been linked to voluntary

movements in early studies (Vanderwolf, 1969), and theories have proposed that it plays a fundamental role in active information sampling (Ekstrom and Watrous, 2014). Indeed, studies have reported significant enhancements in the band's power during active locomotion when compared to passive translation in space (Chen et al., 2013; Terrazas et al., 2005).

In humans, intracranial EEG studies in epilepsy patients have shown theta power increases during virtual movement, although in lower frequencies than the 4-8 Hz band typically observed in the rat (Ekstrom et al., 2005; Watrous et al., 2013b; Jacobs, 2014). The human literature has also linked hippocampal theta to successful memory encoding of information (Lega et al., 2012). In particular, studies have linked pre-stimulus theta to successful learning in word recognition paradigms (Fell et al., 2011). For a review on the critical role of theta oscillations in memory, see Lee et al. (2013).

Does hippocampal theta support active learning in humans? Grounded in the animal literature, we predicted voluntary learning to be characterized by increases in the power of hippocampal theta oscillations during active information sampling. We designed a Virtual Reality (VR) spatial navigation test in which participants first explored and memorized items in a 3D environment under two conditions which differ in their degree of control over navigation (Methods). Later on, they were tested for their memory of those items in a traditional recognition memory test. We employed intracranial EEG recordings from epilepsy patients undergoing seizure monitoring to evaluate differences in spectral power during volitional versus passive memorization.

5.2 Methods

5.2.1 Participants

Participants were 6 epilepsy patients (2 male, 21-38 years) who had been surgically implanted with depth electrodes as part of their diagnostic assessment of surgical treatment for medically refractory epilepsy. The experiment

was conducted with 10 patients, but in 4 of them, the onset of the epileptic seizure was found in the hippocampus and were therefore excluded from the analyses.

As a control experiment, we conducted the same paradigm with a group of 23 human subjects (17 male, age = 25.04 ± 4.92), from Universitat Pompeu Fabra’s student community. All participants provided written informed consent to participate in the study. The protocol of the experiment was approved by the local Ethical Committee “Clinical Research Ethical Committee (CEIC) Parc de Salut Mar” (Barcelona, Spain).

5.2.2 Task description

Subjects navigated a squared virtual environment in which discrete visual stimuli, extracted from (Rossion and Pourtois, 2004), were presented at specific locations in a 5x5 grid formed by red boxes located on the ground (Fig 5.1A, left). When subjects were close to one of the boxes, an item pertaining to that specific location was presented through a small inset on the top-right of the screen (Figure 5.1A, middle). Participants were instructed to visit all boxes and remember all the items for a subsequent recognition memory test.

Critically, subjects explored the environment under two conditions, one with self-initiated, active control of position and orientation in the VR environment and the other a passive exposure mode with no control over navigation. Navigation blocks lasted for 3 minutes and each subject performed three active and three passive. Navigation data in the active mode (i.e., positions and orientations) was recorded at 1000 Hz. The same sequence of observations was then presented to a different subject in the passive mode, who was exposed to the same visual information, following a “yoked” design.

Across subjects, the same trajectory and items were presented in the same order and for the same durations in both conditions (Voss et al., 2011a, Figure 5.1B, bottom). For the first subject in the control experiment, data for the passive condition was recorded from an additional subject who was not included in the analysis. The same data was used for the first subject

in the patient group. However his data was discarded because the seizure onset in the first patient was found in the hippocampus and was therefore excluded from the analysis. We used navigation data from patient 1 in the passive condition of patient 2.

Before the start of the experiment, all subjects underwent a training session, in which they were allowed to freely explore the environment for 2 minutes to familiarize with the interface. In this training session, an example item was shown in all boxes, which was later on excluded from the experiment. The order of the blocks was predefined to start with active or passive and then alternate. Four patients and 11 healthy subjects started with the volitional block (V-P-V-P-V-P), and the other 4 patients and 11 healthy subjects started in passive navigation mode (P-V-P-V-P-V).

There was a 20 seconds pause between blocks, during which a black screen was shown. Positions and orientations at the start of each active block were randomly selected from four possible pre-defined starting points.

After the last encoding block subjects were tested for their memory for the items with a traditional recognition test. Participants were presented with 160 items, of which 40 were previously shown during active navigation, 40 were presented during passive navigation and 80 were new. During the test, an image was displayed on the screen and subjects were asked to indicate whether they had seen it before using a 6 points confidence scale — from 1 (Sure unfamiliar) to 6 (Sure familiar). The confidence question and the image remained visible until participants reported their answers (Figure 5.1A, right). An inter-trial interval of 3 seconds was set between participant's responses and the next test item.

Patients could control navigation with a joystick while sitting in the hospital bed. A 17" inch portable computer was installed on a mobile table from the hospital and distance from the screen was kept constant across sessions at around 60 cm from the subjects. Healthy subjects controlled navigation with a joystick, and the application was deployed in the same portable computer installed in the laboratory.

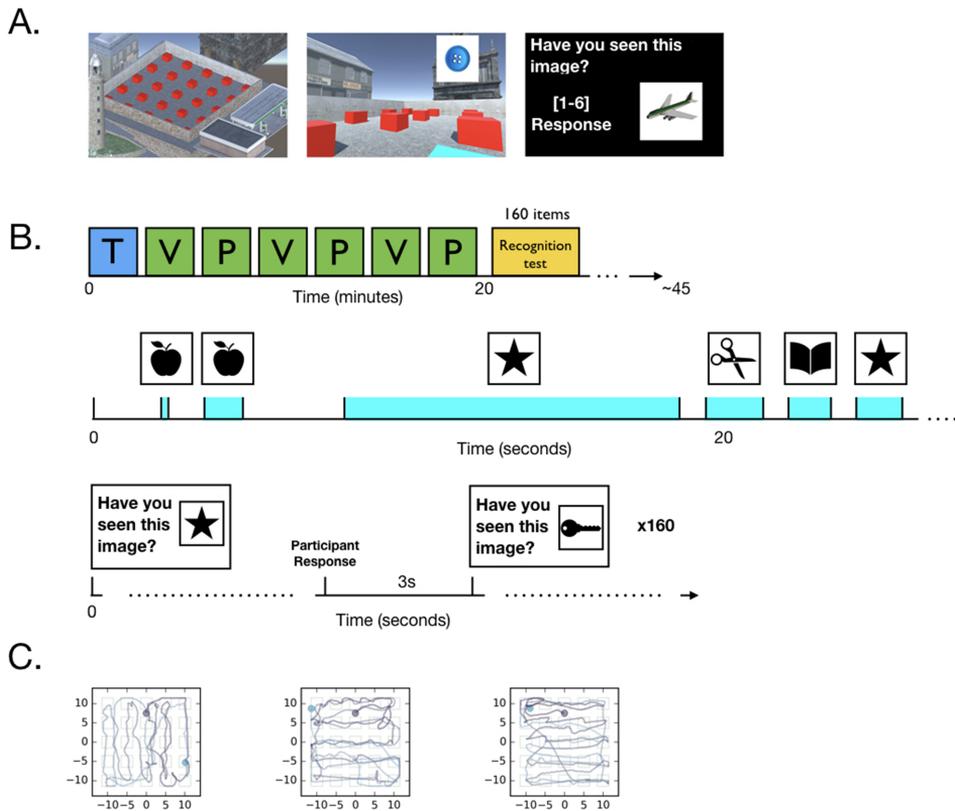


Figure 5.1: Task description. A) Left: layout of the environment. Middle: Stimulus presentation during the encoding phase of the experiment. When a box is “active”, a particular item is presented in the top-left of the screen. Right: At test, an image (old or new) is presented and remains visible until participants report their answers. B) Top: Schematic timeline shows the main blocks of the experiment (V = Volitional, P = Passive). Bottom: Detailed timeline showing the first 30 seconds of navigation of patient 1 in the first volitional block of the experiment. Cyan areas above the timeline indicate the presentation of a stimulus on the screen. Icons depicting stimuli were not part of the test but are included here for illustration purposes. Participants decided on the materials and timings of study on a moment by moment basis, and typically revisited some of the boxes and items. This same sequence of observations was used in the first passive block of subject 2. C) Trajectory of one healthy participant in the three active blocks of the experiment, plotted from an allocentric perspective.

The VR application was created with the Unity3D Game Engine (San Francisco, CA). A timeline of the experiment can be seen in Fig. 5.1B.

5.2.3 Behavioral analysis

To address differences in exposure time to items depending on study conditions, we pooled data into items viewed for extended or short times, i.e., below or above the median of all exposure times for each subject in each condition. All trials with ± 2.5 standard deviations away from the median of the distribution were removed for this specific analysis. In the healthy subjects group, an average of 1.43 trials were excluded from the active condition (range 0-3), and an average of 1.78 from the the passive condition (range 1-3). In the patients, an average of 1.57 trials were excluded in the active condition (range 0-3), and of 2 trials from the passive condition (range 0-4).

For the analysis of Decision Times (DT), from stimulus onset till response in the recognition test, all trials with ± 2.5 standard deviations away from the median for each subject were excluded to avoid influences from partial/spurious views and lapses of attention. This represented a mean of 3.28 excluded trials in the patients (range 1-7) and of of all trials in the patients and of 4.2 (range 1-9) in the healthy participants.

Since subjects reported in general with high confidence, we pooled data from low and medium confidence levels to compare performance in high and low confidence with an equivalent number of trials in each condition (Rutishauser et al., 2015).

We used a two-way repeated measure ANOVA with “memory” (novel/familiar) and “confidence” (high/low) as factors to quantify the relationship with DT. The repeated factor was subject number. For the analysis of volitional versus passive conditions, we built a second ANOVA model with “exposure time” (short/long) and “encoding condition” (volitional/passive) as factors to evaluate their relationship with recognition performance.

For the analysis of DTs, we used a one-way ANOVA with factor item condition (old congruent—old incongruent—new). Pairwise *post hoc* comparisons were performed using paired *t*-tests.

5.2.4 Intracranial EEG analysis

Electrophysiology

Recordings were performed using a standard clinical EEG system (XLTEK, subsidiary of Natus Medical) with 500 Hz sampling rate. A unilateral implantation was performed in all patients, using 7 to 10 intracerebral electrodes (Dixi Médical, Besançon, France; diameter: 0.8 mm; 5 to 15 contacts, 2 mm long, 1.5 mm apart) that were stereotactically inserted using robotic guidance (ROSA, Medtech Surgical, Inc).

Electrode selection

Precise location of electrodes was achieved by our clinical team at the Hospital Del Mar (Barcelona, Spain). Magnetic Resonance Images (MRI) were acquired for every patient before implantation and co-registered with computer tomography (CT) scans after surgery to verify the placement of the electrodes. The presence of specific contacts within the hippocampus proper was visually confirmed via careful examination of the MRI and CT scans. Electrode locations in real space as captured by the scans were converted to MNI coordinates using 3D slicer (www.slicer.org, Pieper et al., 2004), following the method described in (Principe et al., 2017).

Targeted regions varied across patients for clinical reasons, but in all subjects included the anterior or posterior hippocampus. The lateral implantation schema usually included 1 to 3 contacts points within the hippocampus per electrode. In all patients, we subtracted the activity of the two deepest contacts to obtain a bipolar reference.

Spectral Power

We band pass filtered the signal for the selected electrodes from 1 to 200 Hz using EEGLab (Delorme and Makeig, 2004). Before decomposing the signal, we applied an automatic artifact rejection method to exclude periods in which the filtered iEEG signal was above 2 Inter Quartile Range (IQR) of the median of the navigation periods and visually inspected the signal to manually remove the remaining artifacts. After artifact removal, we decomposed the signal of the whole experiment using complex Morlet Wavelets with a variable number of cycles (min: 3, max: 10), in 1Hz steps for the frequency range between 1 and 29Hz, and 5Hz steps for the 30-100Hz range. The resulting time-series of frequency-specific power were then z-transformed to the mean and standard deviation of all navigation blocks combined. This was done individually per frequency and participant.

We compared active versus passive power by averaging values in the 2-7Hz band for each block type and subject separately. At the group level, we compared subject averages by the means of paired *t*-tests. We included a control condition in which participants observed a black screen during the pauses between navigation blocks of the experiment.

We used cluster statistics to correct for multiple comparisons at the group level in the all-frequencies analysis reported in Figure 5.5. Basically, we shuffled the labels of the subject averages of each condition 1000 times and performed paired *t*-tests to generate a distribution of clusters (and average *t*-values) to be expected by chance. We then contrasted the average *t*-value from the observed 2-7 Hz cluster with the distribution of the generated *t*-values to obtain a *p*-value.

5.3 Results

5.3.1 Results control experiment

We aimed to evaluate recognition performance in a group of healthy young adults (N=23) before conducting the paradigm with the patients. Grounded

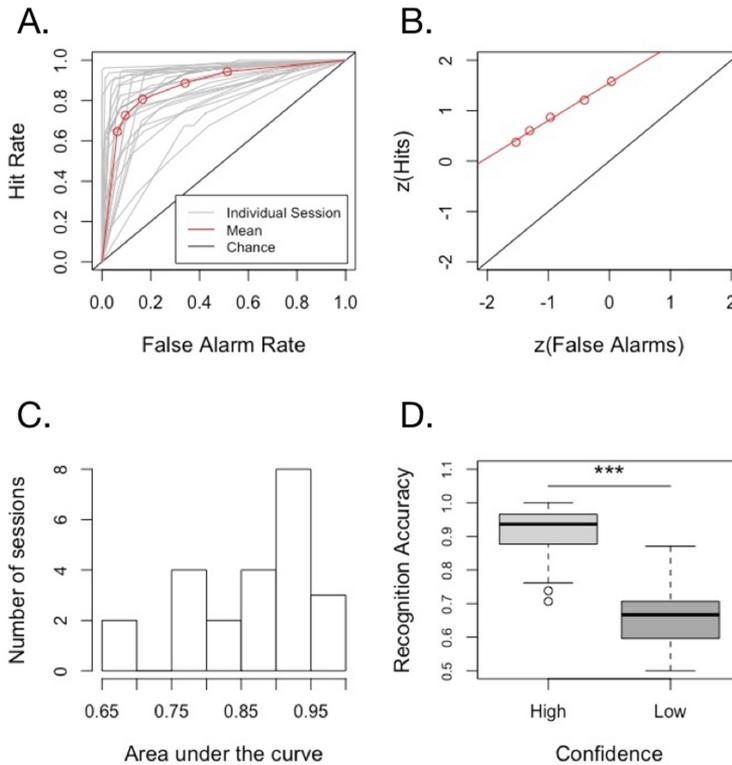


Figure 5.2: Overall Results from control experiment. A) Behavioral ROC curve for individual sessions ($N = 23$, grey) and average (red). Each data point is a different confidence level. B) z-Roc curve from the same data. C) Histogram of the AUCs. D) Recognition accuracy (normalized), as a function of confidence. Accuracy was significantly higher for high as compared to low-confidence trials ($p < .01$, paired t-test).

in the literature, we hypothesized to find better recognition performance for items encoded in the volitional condition.

Overall results

Using traditional methods in the scientific study of recognition memory, we conducted a Receiver Operating Characteristic (ROC) analysis for each participant, to assess how well they discriminated old and new items in the recognition test (Squire et al., 2007). All participants performed above chance level (0.5 for Hits and False Alarms, along the diagonal in Figures 5.2 A, B) at different levels of confidence. The average area under the curve (AUC) was 0.86 ± 0.02 (SE, Figure 5.2C). As expected for declarative memories (Kahana, 2012), the z-ROC curve was asymmetrical along the chance diagonal (mean z-ROC slope = 0.74), indicating a greater variance in the distribution of the old items memory strength (Squire et al., 2007).

Participants responded in general with high confidence (62.5% of the trials, SD = 26.7%); medium and low confidence were assigned less frequently and in similar proportions (M = 17.1%, SD = 1.4% and M = 20.2%, SE = 14.7% respectively, Figure 5.2 C). Due to this unequal distribution, we pooled data from trials with intermediate and low confidence ratings for a comparison between high and low confidence with an equivalent number of samples (Rutishauser et al., 2015). Normalized accuracy was significantly higher in the high confidence group $t_{(22)} = 11.24$, $p < 0.001$, $d = 2.34$, Figure 5.2 D.

Volitional versus passive learning

Subjects showed increased performance for information acquired in the volitional as compared to the passive condition in the memory test. Items studied actively were recognized significantly better (volitional: M = 0.84, SD = 0.12; passive: M = 0.76, SD = 0.16, $F_{(1,22)} = 5.9$, $p < .05$, $\eta^2 = 0.21$, Figure 5.3A), and participants responded with higher levels of confidence in the active as compared to the passive condition, $F_{(1,22)} = 5.4$, $p < .05$, $\eta^2 = 0.19$, Figure 5.3B.

Although across subjects the same items were observed by the same amount of time, we checked whether exposure time to items interacted with study condition or modulated recognition performance independently.

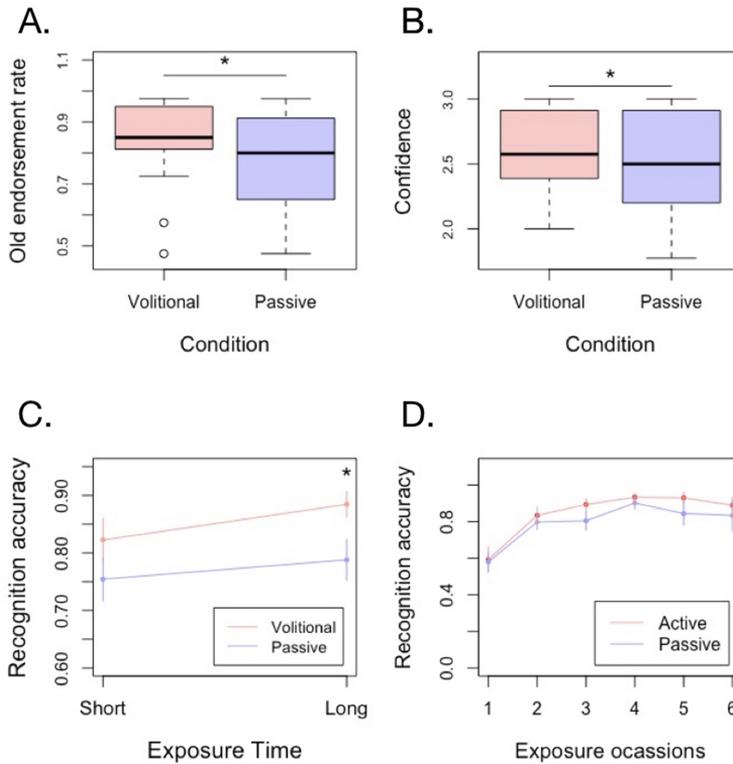


Figure 5.3: Self-directed learning benefits memory A) Recognition accuracy as a function of encoding condition (i.e., volitional vs. passive). Accuracy was significantly higher for items learned in the active condition. B) Confidence as a function of encoding condition. Subjects responded with higher confidence to items encoded volitionally. C) Recognition accuracy for volitional and passive trials as a function of exposure time to items (median split). D) Recognition accuracy as a function of number of independent exposures to items (one visit or revisiting). * indicates $p < .05$.

We calculated a median split on study duration for each test item and assessed performance for both short and long categories separately (Methods). Our results revealed a main effect of exposure time to items which did not interact with encoding condition (exposure time: $F_{(1,22)} = 8.85$, $p < .01$, $\eta^2 = 0.28$; exposure time - encoding condition interaction: $F_{(1,22)} = 1.68$, $p = .20$, $\eta^2 = 0.07$, Figure 5.3C).

Post-hoc tests revealed a tendency for items studied for short periods of time to be recognized significantly better in the active condition $t_{(22)} = 1.77$, $p = 0.09$. At long exposure times, the effect reached significance $t_{(22)} = 2.93$, $p < .05$.

We also observed an effect of exposure time on the confidence levels, $F_{(1,22)} = 15.18$, $p < .01$, $\eta^2 = 0.40$. This effect was independent from the encoding condition effect (exposure time - encoding condition interaction: $F_{(1,22)} = 0.58$, $p = .45$, $\eta^2 = 0.03$, Figure 5.3C).

We did not find significant differences in performance or confidence related to the number of visits across conditions. We did observe a general trend for recognition accuracy to increase with the number of visits to items (Figure 5.3D).

5.3.2 Behavioral results patients group

Overall results

ROC analyses revealed that, at all levels of confidence, discriminability was above chance (along the diagonal in Figure 5.4A). The AUC was 0.851 ± 0.1 . Participants adequately assessed the quality of their memories: recognition accuracy was increased for high confidence trials as compared to low confidence ones, High: 0.86 ± 0.13 , Low = 0.66 ± 0.06 ; $t_{(5)} = 5.93$, $p < 0.01$, Figure 5.4B.

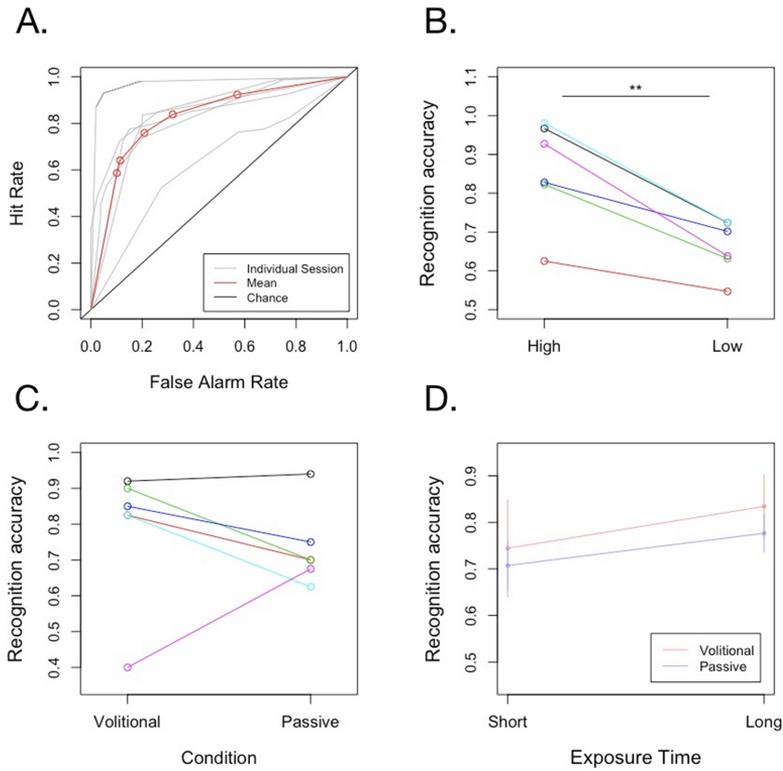


Figure 5.4: Behavioral results iEEG experiment

A) Behavioral ROC curve for individual sessions ($N = 6$, gray) and average (red). B) Recognition accuracy as a function of confidence. C) Recognition accuracy as a function of encoding condition (i.e., voluntary vs. passive). D) Recognition accuracy for volitional and passive trials as a function of exposure time to items (median split).

$p < .001$

Volitional vs. passive learning

Five out of 6 participants performed better in the active as compared to the passive condition. At the group level, we did not find significant differences between the two conditions, $F_{(1,5)} = 0.34$, $p = .58$ (Figure 5.4C). We did observe a tendency for subjects to perform better at long exposure times ($>$ median), $F_{(1,5)} = 4.52$, $p = 0.08$ (Figure 5.4D). No interaction between exposure time and encoding condition was found $F_{(1,5)} = 0.02$, $p = 0.8$ (Figure 5.4D).

5.3.3 iEEG results

Hippocampal power during active learning

We quantified hippocampal low-frequency power during the encoding phase of our experiment, including all navigation time points during active and passive navigation, and a control condition in which subjects were exposed

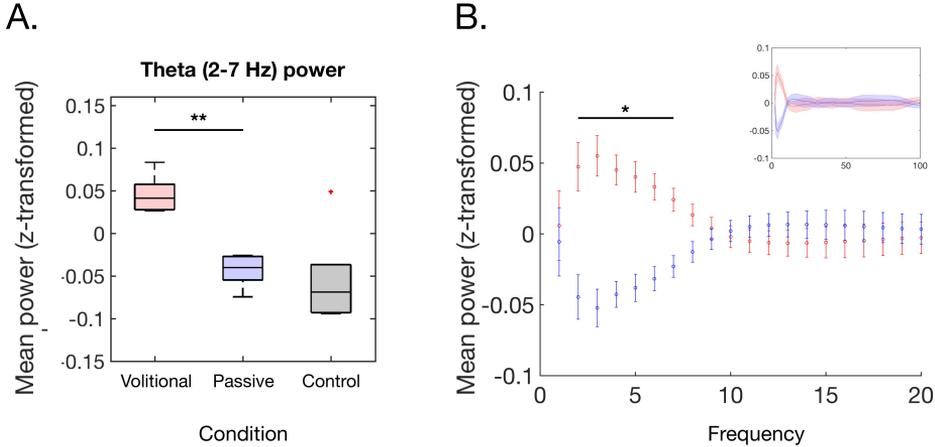


Figure 5.5: Theta power increases during active as compared to passive navigation in the human anterior hippocampus.

A) Mean theta power during active, passive and a control condition (black screen viewing). B) Frequency-specific (1-20Hz) z-power. Significant differences were observed in a cluster from 2-7Hz (black line). The inset shows the same analysis extended until 100 Hz.

* = $p < 0.05$. ** = $p < 0.01$.

to a black screen in the pauses between navigation blocks. We found that irrespective of performance in the memory test, there was a significant main effect of encoding condition in the observed hippocampal Z-scored theta power (2-7 Hz, $F_{(2,10)} = 7.65$, $p < .01$). *Post hoc* tests confirmed that theta power observed in the anterior hippocampus during the active blocks was significantly higher than in the passive blocks, $t_{(5)} = 5.43$, $p < .01$ (Bonferroni Corrected, Figure 5.5A). We observed a marked tendency of increased theta oscillations in the active navigation as compared to the control condition (black screen), which did not reach significance after Bonferroni correction $t_{(5)} = 2.93$, $p = .06$.

The individual frequency analysis revealed a significant cluster of contiguous frequencies that reached significance between 2 and 7 Hz with a peak at 4Hz (see Supplementary Material Table 5.1 for the statistics conducted over each frequency). The average t -values of this cluster survived multiple comparisons correction using cluster statistics (Maris and Oostenveld, 2007; see Methods, Figure 5.5B).

5.4 Discussion

We have investigated the neural correlates of self-directed learning and its role in the modulation of human recognition memory. We operationalized self-directed learning as the continuous voluntary control over information intake during knowledge acquisition, and hypothesized that items memorized under this condition would be recognized significantly better than those learned passively. At a physiological level, we predicted active learning to be characterized by increases in the power of hippocampal theta oscillations.

Results obtained across our two experiments confirmed our hypotheses. Our control setup demonstrated a clear effect of volitional learning in recognition performance, which was observed in the increased old endorsement rate (correct responses) for items encoded in the active as compared to the passive condition. Moreover, our results revealed that participants reported their responses with higher levels of confidence in trials encoded volitionally. Al-

though in the patients' group, differences in recognition accuracy between conditions did not reach significance, we observed a similar tendency, with more variability given the decreased N size. We conducted a between-groups analysis to check for systematic differences in mnemonic performance and did not find evidence for impaired memory in the patients as compared to the healthy controls (no significantly different AUCs between the groups, $p > .05$).

Our behavioral results are consistent with the human literature, in which self-paced learning has been consistently associated with mnemonic benefits in humans (Gureckis and Markant, 2012).

On the other hand, our iEEG findings revealed frequency-specific increases of hippocampal oscillatory power in the active as compared to the passive condition. In particular, we observed significant increases in a frequency range between 2 and 7 Hz, with a peak at 4 Hz, while activity above that threshold was unaffected. We also found a marked increase in theta during active navigation as compared to the control condition in which subjects looked at a black screen. Analysis of the individual data revealed that the difference between active and passive navigation conditions was observed systematically across all participants in the 2-7 Hz band (data not shown). The same was true for the active versus control comparison.

These results are consistent with the role of hippocampal theta in exploratory or *active sampling* behaviors observed in the animal literature. Indeed, power in the 4-8Hz band has been reported to increase when rats engage in whisking and sniffing aimed at acquiring sensory stimuli, but not when animals merely whisk in the air (Berg et al., 2006; Macrides et al., 1982; Colgin, 2016). Although rodent hippocampal theta power increases are typically at higher frequencies (i.e., in the 4-8Hz band), it has been argued that a functionally equivalent in humans might involve the 1-4Hz Delta band (Ekstrom and Watrous, 2014).

Our findings can also be considered as an extension of previous brain imaging work aiming to identify the neural correlates of active learning in humans

(Voss et al., 2011a,b). These investigations have pointed to the hippocampus as playing a critical role given its increased BOLD activations during active as compared to passive learning. Our results add to those findings the detailed time-frequency characteristics of the process in the hippocampus.

Our results are also in line with previous human iEEG studies which have explored the role theta oscillations in more conventional recognition memory tasks. In particular, increases in pre-stimulus theta power at encoding have been reported to predict successful memory formation (Fell et al., 2011). In preliminary analysis we did not observe transient increases in theta power time-locked to the presentation of the stimuli (data not shown), but a rather continuous and systematic increase that is observable in time-periods extending minutes. Whether the tonic increases in theta can be linked to memory improvements will remain to be determined in future research.

Finally, the increase in hippocampal theta we observe is consistent with a role of the hippocampus acting as a “hub” during memory encoding, linking parietal and cortical areas in the service of memory formation (Voss et al., 2011a). Speculatively, it is possible that the hippocampal low-frequency oscillations we observe coordinate communication across brain regions during memory encoding, as has been shown during mnemonic retrieval, with different frequency bands carrying different types of information (Watrous et al., 2013b).

In summary, our findings provide evidence of the power of self-directed learning in enhancing subsequent recognition memory performance at a behavioral level, and show the critical role of theta oscillations in the human hippocampus during the process.

Table 5.1: Table indicates t - and p -values in the active versus passive comparison for each frequency in the hippocampus.

Frequency	p	t
1	0.82408	0.23425
2	0.037698	2.8066
3	0.011364	3.904
4	0.0065436	4.4759
5	0.01227	3.8282
6	0.014621	3.6583
7	0.029606	3.0144
8	0.13906	1.7581
9	0.62632	0.51836
10	0.80035	-0.2667
11	0.54373	-0.65108
12	0.4828	-0.75768
13	0.49895	-0.72857
14	0.53772	-0.66121
15	0.58239	-0.58751
16	0.6298	-0.51301
17	0.67752	-0.44116
18	0.72219	-0.37621
19	0.76132	-0.32083
20	0.79279	-0.2771
21	0.81404	-0.24794
22	0.82438	-0.23384
23	0.82813	-0.22874
24	0.83478	-0.21972
25	0.85703	-0.18967
26	0.90722	-0.12258
27	0.98875	-0.014824
28	0.91591	0.11103
29	0.83966	0.21311
30	0.80302	0.26303
31	0.99498	-0.0066112
32	0.82923	-0.22725
33	0.9554	0.058791
34	0.90104	0.13079
35	0.81482	-0.24688
36	0.74414	-0.34499
37	0.75514	-0.32949
38	0.73526	-0.35758
39	0.66664	-0.4573
40	0.62239	-0.52443
41	0.71334	-0.38893
42	0.99777	0.0029411
43	0.60795	0.54691
44	0.36508	0.99577

Spatializing experience: a framework for the visualization and exploration of historical data using VR/AR systems

Throughout this dissertation, we have investigated human memory from a scientific perspective, in tightly controlled experimental situations. However, this knowledge is more valuable if, beyond an intellectual exercise, it can also be applied in real-world systems. In the last two chapters of our dissertation, we describe a novel framework for human-data interaction in the field of Digital Heritage, which is inspired in the concepts of active learning and context-dependent memory. Our platform facilitates the spatialization of information in virtual and real-world scenarios, and the active engagement of users in the exploration and learning of historical of data. In this chapter, we present the main

components of our architecture and introduce a recently developed hand-held application for the spatial interaction with geolocalized datasets. Our AR learning tool can be seen as a *proof of concept*, a first step to bridge the gap between knowledge of memory acquired in the laboratory and real world educational technology. This chapter reproduces a study entitled “Spatializing experience: a framework for the geolocalization, visualization and exploration of historical data using VR/AR technologies”, which was published in the *proceedings of the 2014 Virtual Reality International Conference* (Pacheco et al., 2014). The abstract reads:

In this study we present a novel Information and Communication Technologies (ICT) framework for the exploration and visualization of historical information using Augmented Reality (AR) and geolocalization. The framework facilitates the spatial localization of multimedia files, as well as their later retrieval and visualization through an AR paradigm in which a virtual reconstruction is matched to user’s positions and viewing angle. The main objective of the architecture is to enhance human-data interaction with cultural heritage content in outdoor settings and generate more engaging and profound learning experiences by exploiting information spatialization and sequencing strategies. We worked in collaboration with the Bergen-Belsen memorial foundation, who administer the former concentration camp grounds of the same name to design and implement an information augmented space in the outdoor environment that can be navigated both in space and content using a hand-held tablet device. Our tablet application aims to enhance the experience of the visitors of the memorial, to improve their understanding of the historical facts that took place there, and to facilitate the construction of meaning from this knowledge with respect to their own experience. The platform developed in parallel to

this application demonstrates a valuable set of integrated elements such as reconstruction, content database interaction, and spatialized narratives.

6.1 Introduction

One of the key challenges in the field of Human Computer Interaction (HCI) is to develop information systems that can help us to make sense of big amounts of data (Pirolli, 2007). Particularly in the field of historical research, with the increase of public access to cultural heritage databases (Concordia et al., 2010), this challenge addresses also the public interaction with vast amounts of information, generating a need to update guidance and interpretation systems. With the advent of mobile devices and ubiquitous computing, a relevant area of research has become the study of methodologies to distribute information in the physical space, applying geolocalization technologies (Avouris and Yiannoutsou, 2012). Recent developments of mobile Augmented Reality systems have focused in spatial navigation, including physical movement in an environment, as a novel paradigm to organize the interaction with content (Aart et al., 2010) or filter information density (Keil et al., 2013). Both developments need further research and are partially assessed by the platform described in this document. In addition to the description of our framework, its basic functionality and main structures in Section 7.3, we present the first implementation of the architecture in section 6.3. In section 6.4 we discuss our methodology, conclusions and future work.

6.1.1 Bergen-Belsen case

The platform and tablet application presented here were developed in collaboration with the Bergen-Belsen memorial in Germany, which offered us the availability of a historical outdoor environment, as well as a large amount of historical content material from the memorial's archive that refers to multiple locations in that environment. Bergen-Belsen is a former WWII concen-

tration camp in northern Germany from which most architectural structures were burned down shortly after its liberation in april 1945 to avoid the spread of a typhus epidemic. Today, the site is a nature park hosting a number of memorial structures, mass graves, and memorial foundation buildings. Information about the camp can be found in documents, books, and a permanent exhibition in the documentation center of the Bergen-Belsen Memorial. Yet, onsite there are nearly no physical remains of the original structures, and visitors largely depend on their imagination to reconstruct the topology of the camp and connect the tragic events that took place there. Both the Augmented Reality application and the broader framework described in this paper aim to fill this gap through the use of novel Information and Communication Technologies (ICTs).

6.2 Framework description

6.2.1 Overview

The platform presented in this section consists of a number of core elements that integrate into the hand-held tablet application discussed in section 6.3. In the following paragraphs, we introduce a platform concept applicable to more applications than that one: a geolocalized 3D virtual reconstruction that constitutes a navigable entry point to a geolocalized historical database. Navigating in this virtual reconstruction allows users to access historical documents like diary extracts, photographs, drawings, audio fragments, and more. The presentation at real-world coordinates of these documents is made relative to the position of the user and their historical reference.

6.2.2 Historical sources

The application database constitutes a searchable structure developed in SQLite. It allows for the organization of and interaction with historical content items, as well as the association of these items to coordinates in the real world environment. The content of the database is constituted by historical documents in the form of digitized multimedia files. Core element in this or-

ganization are metadata-sheets, that store multiple information fields based on the documentation center's existing archive filing system. These metadata sheets provide the essential link between database search and on-site navigation. Next to hosting a growing corpus of content items, the database also includes items that provide contextual connections between numbers of them, such as interpretative and guiding texts and brief introductions. For this application, part of the memorial's existing exposition and catalogue texts were deployed. A dedicated web application was devised to facilitate the selection, addition and editing of content and metadata in the platform database by experts of the memorial foundation themselves. Next to facilitating a parallel workflow for collaboration between historians and platform developers, this application proved also a method to advance development and testing using metadata while the content itself, or the rights to use it were not yet cleared, which proved a very common case in practice. The web application is directly connected to the database, and therefore edits made in the web also affect how content is deployed and displayed in the client tablet application used in the field.

6.2.3 Virtual Reconstruction

As topographical basis of the platform and its applications, a virtual reconstruction was made of the former concentration camp. Since the camp existed between 1938 and 1945 and its complex history includes many different uses, inhabitants, buildings as well as sub-sections, its reconstruction cannot be generated as a model of one single state, an common issue in other historical reconstruction modeling cases (Tan and Rahaman, 2009). To address this issue, spatial items were identified in a way similar to a cadastral register. Each 3D model carry metadata storing information on its state and use relative to points in time. The 3D reconstruction that is generated and rendered from prepared models is thus composed from the momentary state of the whole of elements at the requested moment in the timeline. This database-approach prepares also for the association of content items to historical spatial items, next to their association to real-world

coordinates. This approach also assesses another common issue in the practice of historical reconstructions: that of uncertain, inaccurate, ambivalent, or incomplete information (Koller et al., 2009). In this platform application, a *Master model* is conceptually separated from its public *Exposition* derivative, the latter representing a style and level of information detail that is found suitable for the public, while the first seeks to integrate all information available – including uncertain and discussed elements. The *Master* version in the Bergen-Belsen case integrates all kinds of information, from available historical as well as current maps and geographical data, photographs, blueprints, witness descriptions and drawings. The *Master model* is therefore a model state that is essentially by default open for discussion and updating, while its *Exposition* version is an application-specific, fixed derivative of it. Moreover, the looks of the latter version are not only defined by the level of most-trusted information about its elements, but also by the required style for optimal use in a public application, which can result in a deliberate limitation of element fidelity such as material colors, light conditions, building and texture detailing. However, the challenge of coping with and representing relative information uncertainty with regard to reconstruction modeling is considered to be not yet sufficiently met and requires more research and development than shown in this platform application.

6.2.4 Applications

Content database, spatial association via metadata, and reconstruction come together in a visual representation with which a user navigates, both in space, content, and history. Thus far, two applications have been deployed that demonstrate this integrative platform characteristic. A first prototype was implemented as immersive indoor installation at the memorial's entrance square, depicting the reconstruction on a 180 degrees screen projection as part of an introductory presentation to the memorial site and its history. In next section, we further discuss the hand-held version of the platform.

6.3 Hand-held Application

6.3.1 Overview

To deploy the integrative platform architecture, a site-specific tablet application was developed to a) enhance a visitor's experience of a visit to the memorial's outdoor area — an approx. 1km² nature park with little to no remains of the former camp — by offering a geolocalized visualization of the camp's reconstruction, combined with a content navigation tool, and b) to research the possibilities of using space and spatial navigation as a novel paradigm to organize education and storytelling in the context of cultural heritage. The application described here integrates database interaction, reconstruction modeling and content presentation in a hand-held device following an Augmented Reality paradigm to be used by visitors on-site. iPads were chosen as tablet hardware, and most software was implemented using the multi-platform Game Engine Unity3D¹, which offers state-of-the art possibilities for 2D and 3D graphics visualization.

6.3.2 Database implementation

A limited amount of archive content was selected by the memorial's history and education colleagues and submitted to the platform's database structure. Metadata for these items was also entered for 30 fields, of which the 4 most important ones, (title, author, description, and reference) are currently applied in the on-site interaction. Origin and reference locations were entered and made available using the dedicated web application of the database. An embedded online map implementation that allowed users to simply click on a location to associate latitude and longitude coordinates to the relevant item. This implementation made it possible to quickly place, edit and relocate content points (POCs), as well as generate a simple grouping of them, in Points of Interest (POIs). The latter allowed for the generation of area-related groups and basic routes.

¹www.Unity3D.com

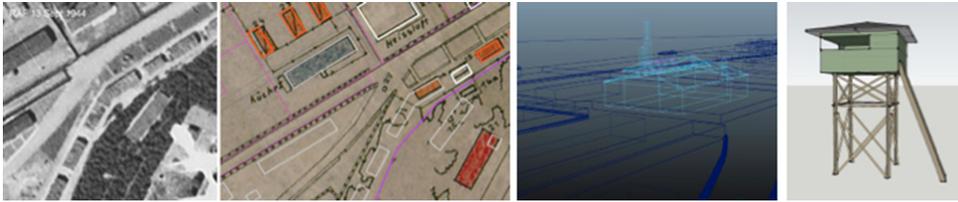


Figure 6.1: Example 3D models. From left to right: 1944 aerial photograph of the camp (IWM London), 1943 presumed building plan by Heeresbauamt, virtual model of Delousing building and final version of an outside fence watchtower.

6.3.3 Reconstruction implementation

The reconstructed states of the former camp site were limited to two moments in its history: September 1944, and April 1945. Both moments are already central in the memorial's exposition and catalogue, and information as well as content materials related to the environment at these moments was more available than for earlier periods. The reconstruction of the two states was performed by integrating a body of research by the memorial experts themselves, together with several maps, photographs, drawings and descriptions into master model files. 3D modeling was based on the integration of information in blueprints, photographs, drawings and descriptions, and performed using programs Autodesk Maya² and Sketchup³ (Fig 6.1). Available maps were matched to geodesically corrected and combined historical aerial photographs (Thomas Kersten, 2004; Hummel, 2008) as well as the present day satellite imagery used for the tablet's global positioning system (GPS). The generated master maps describe buildings, fences and other spatial objects and areas as vector objects that can at all times be compared to historical source layers. This first process step was performed using a combination of AutoCAD, Adobe Illustrator and Photoshop. The vector master maps subsequently served to place and size 3D models as accurate as historical sources and expert interpretation could offer, and construct a virtual environment. The represented model style developed from

²www.autodesk.com

³www.sketchup.com



Figure 6.2: The Augmented Reality effect. Through the hand-held device, user can see virtual reconstruction placed in real world coordinates.

a initial estimate-photorealism to a deliberately minimal, desaturated and more abstract style. The reconstruction was equalized to a basic level of plausible form, avoiding the invocation of a immersive experience based on speculation. Differences and uncertainties were discussed and solved in close collaboration with the memorial's experts.

6.3.4 Sensors

The video stream (1920x1080) from the iPad's in-built camera, the in-built GPS, compass, and gyroscope sensors of the iPad are used as inputs to the Unity application. GPS uses a refresh rate of 200 milliseconds and has an accuracy of around 2-3 meters. Compass is used to recalibrate Gyroscope and align the virtual environment with real cardinal points.

6.3.5 User Interface

The application offers two view modes to navigate space and content: Map, and Field view (Fig. 6.3). In both cases, the shown state of the reconstructed

site is made dependent on the chosen historical period. Map view offers an overview of the entire area as well as the historical sections of the former camp. Subjective to choice, the map can be made to rotate automatically to align with North (egocentric navigation), or to remain fixed independent of the user's position and angle (allocentric navigation). Field view offers a look on the site from an average-height 1st-person perspective, showing buildings, fences and other objects in a 3D projection. In this mode, the user can switch between Virtual, and Augmented reality modes, the latter offering to superimpose the reconstructed building and fence models on the iPad's camera image, effectively comparing past and present states.

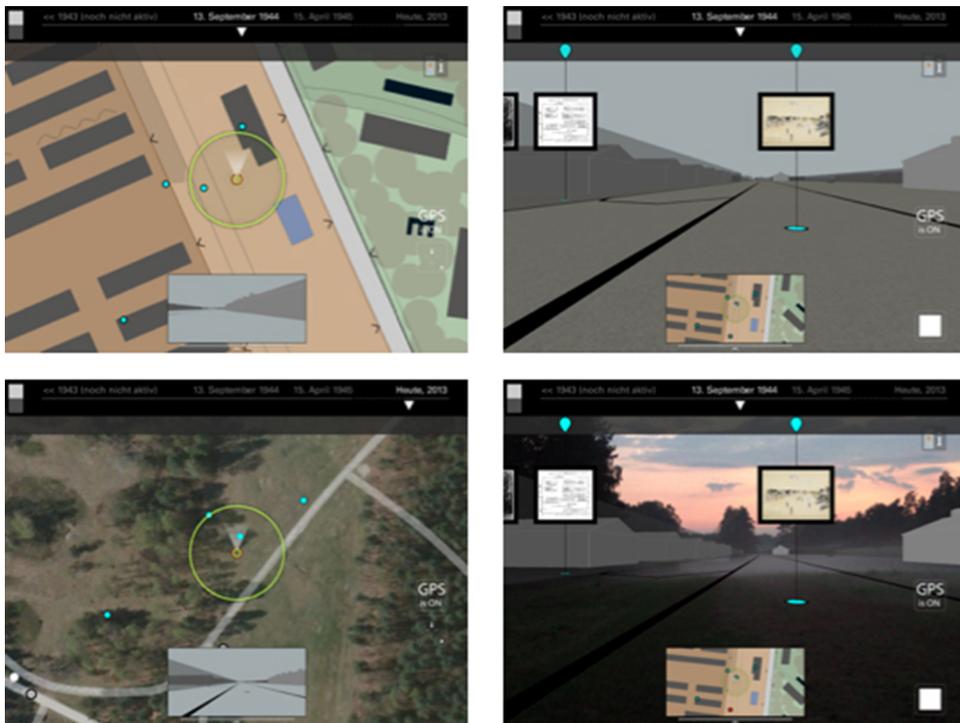


Figure 6.3: Four views of the AR interface. Top left: Map View showing a 1944 state. Bottom left: Current day Map View with POCs. Top right: Virtual Reality Field View with available POCs previews. Bottom right: An Augmented Reality superposition on the local camera view.

6.3.6 Content placement and presentation

As a first step towards situated historical content sequencing, content presentation was disassociated from offering total availability. In the main platform concept, points of content (POCs) are hidden and revealed under controllable conditions, to facilitate different kinds of content interaction in an environment.

As a first step to further dissociate reference locations of content from presentation locations in the environment, POCs were grouped to Points of Interest (POIs). In this manner, sets of content can be grouped, for instance thematically or topographically, and made available from positions other than the content's actual placement. The latter possibility offers an important control on the user's required position in the outdoor, partly forested environment. Two modes were implemented for the presentation and assessment of POIs: Free, and Guided exploration. In the Free mode, all POIs are made visible to a user in the environment, but the associated content items can only be assessed when one is near enough. This proximity condition is implemented and communicated using a wider circle around the user's locator on the map. In the Guided exploration mode, not all POIs are made visible at the start, but they are revealed stepwise, with the same proximity condition applying after points became visible.

POCs as well as POIs communicate the different state of availability (e.g. Sleeping / Calling / Active / Visited) by color changes of the marker icons visible on the map, and in the field view. In the latter, the user is assisted to find these points by a top bar that shows the direction of a marker where one is still too far to be seen in the virtual reality perspective. If a POC is active, meaning that its content is available, a preview window of the content is presented that can be clicked to open the content. A full screen mode makes the content available to the user, revealing also its caption sheet containing metadata information. This sheet can be slid aside to have a clear view of the content alone.

6.4 Discussion

We have presented a platform solution to enhance public heritage experiences by the integration of historical database content, environment reconstruction, and navigation in outdoor environments. We introduced the first deployment of this platform in the Bergen-Belsen Augmented Reality application: a mobile, on-site, guide/companion tool for the geolocalization, visualization and exploration of historical data about the former concentration camp. We presented the component architecture of the platform and application, revealing a structure to facilitate the ongoing development of spatial narration. The first tablet version of the application is currently being tested with public in the memorial's landscape environment. The integrative development process show that the application is valuable tool for professional users like the memorial's researchers and guides, next to one for visitors, since it offers the comparison of many historical files that until now were accessed at separate moments, at single, spatially related place, together with the outdoor local spatial dimensions.

A number of challenges emerged during development. We continuously encountered different forms of information uncertainty in the digital reconstruction and the geolocalization of the historical sources. This pointed to the importance of finding ways to register and communicate such intrinsic uncertainty in the presentation to the user, rather than hiding or replacing it with speculative solutions. Another important observation, is the hitherto little researched relation between content reference location, and its presentation location in an outdoor environment. In practice, historically correctly located content proved to be sometimes hard to access due to the current-day landscape characteristics like trees or high wet grass. Similarly, the moment of presentation during a tour or exploration depends on content and historical narrative factors. These challenges point to include environmental, and effort-dependent parameters into the platform's envisioned increasingly automatic generation of narrative routes. In extension to that, we plan to include a more elaborate interpretation and learning of user states by the application, as available technologies offer great opportunities to exploit

real-time, interactive mechanisms for guidance and dynamic content environments. One of the first challenges to meet in that context is to identify effective machine learning strategies to infer dynamic user states from the application sensor system, for instance inferring relative attention from combinations of position, viewing angle, and acceleration data. Finally, we also believe the application has the powerful opportunity to reflect and integrate multiple users' experiences into that of one. By tracking the itineraries of different users and inserting them in the database, the system could be able to make decisions based on previous user's choices, which will constitute the first step for the generation of a collective experience in exploring the data in a shared way. This becomes particularly relevant in the context of open cultural heritage, where collective commemoration has public relevance.

6.5 Acknowledgements

This research received funding from the European Community's Seventh Framework Programme (FP7-ICT-2009-5) under grant agreement n. 258749 [CEEDS].

A Location-Based Augmented Reality System for the Spatial Interaction with Historical Datasets

In our final chapter, we provide a more detailed description of our Digital Heritage platform, and show that our AR hand-held application can be a valuable tool to investigate human behavior in real-world settings. We present the results of a pilot study in which we compared active and passive modes of navigating an information augmented outdoor space.

This chapter reproduces a study entitled “A Location-Based Augmented Reality System for the Spatial Interaction with Historical Datasets”, which was published in the *Digital Heritage International Congress (DigitalHeritage)*, 2015, IEEE (Pacheco et al., 2015). The abstract reads:

The key role that space and spatial organization of content play in memory has been taken very little into account in the design of human-data interaction systems. Here, we present a loca-

tion based Augmented Reality application for the exploration and visualization of historical files, which is based on the argument that the embodied interaction with content by moving in the real, physical space will enhance its recollection from memory and comprehension. Our software architecture integrates a historical 3D reconstruction with geo referenced historical documents, as well as specific guidance components for narrative generation. All content of the application database is spatialized and can be navigated in a completely free/exploratory mode or in a passive/guided mode. We present the results of an experiment comparing spatial memory performance in the two modes. Our data confirms previous findings in the spatial navigation literature, suggesting that active exploration of an environment leads to a better spatial understanding of it.

7.1 Introduction

The importance of spatial behavior and physical movement in memory processes is widely acknowledged in the psychological literature (Hupbach et al., 2008; Godden and Baddeley, 1975; Miller et al., 2013a; Chrastil and Warren, 2012). Yet, in the Digital Heritage field, such components have not been taken sufficiently into account in the design of human data interaction systems. This challenge led our group to conceptualize a novel application for the integration of historical sources and space, which aims to foster the generation of meaning from data by promoting active learning in the outdoor environment. Using a free exploration paradigm in the information seeking process (White and Roth, 2009; Bates, 1989), our application is based on a constructivist and situated learning perspective in which learners actively construct their own knowledge, instead of passively receiving information from a teacher or guide (Schrier, 2006; Ackermann, 1996). In our view, a specific *location in the space* — virtual, real, augmented —, is used as the container of different types of historical knowledge — sources, contexts, narratives —, and active exploration of such documents in that container is

what allows users to elaborate individual interpretations and meanings from them.

In section 7.3 we describe our software architecture. In section 7.4 we report the main interaction design decisions we made during the development process. In section 7.5 we present the results of an experiment in which we compared two different modes of data navigation (Free VS Guided). Finally, in section 7.6 we present our conclusions and future work.

The context chosen to test the application concept was the Bergen-Belsen memorial, situated in Lower Saxony in Germany. Bergen-Belsen is a former nazi concentration camp from which most architectural structures were burned down after WWII. The application was developed with the aim of enhancing visitor's experience in the museum outdoor area by offering a localized virtual reconstruction of the place in 1944 and 1945, augmented with content from the memorial's archives.

7.2 Related Work

Our application seeks to integrate a number of key developments in the Digital Heritage field, including a geo localized 3D virtual reconstruction (Papiannakis et al., 2005; Callebaut and Sunderland, 1998), onsite database access of content (Keil et al., 2013; Hable et al., 2012; Aart et al., 2010), and mobile Augmented Reality (AR) (Reponen et al., 2012; Wojciechowski et al., 2004) (for a review see (Noh et al., 2009)). On the other hand, it also incorporates features that are common to state of the art commercial mobile applications for data geolocalization. For instance, current generation AR browsers such as Junaio, Wikitude or Layar, allow users to access contextually relevant information at their proximity, and include features to organize data in tours or define the sequence in which geo-tagged documents are made visible and accessible to the users.

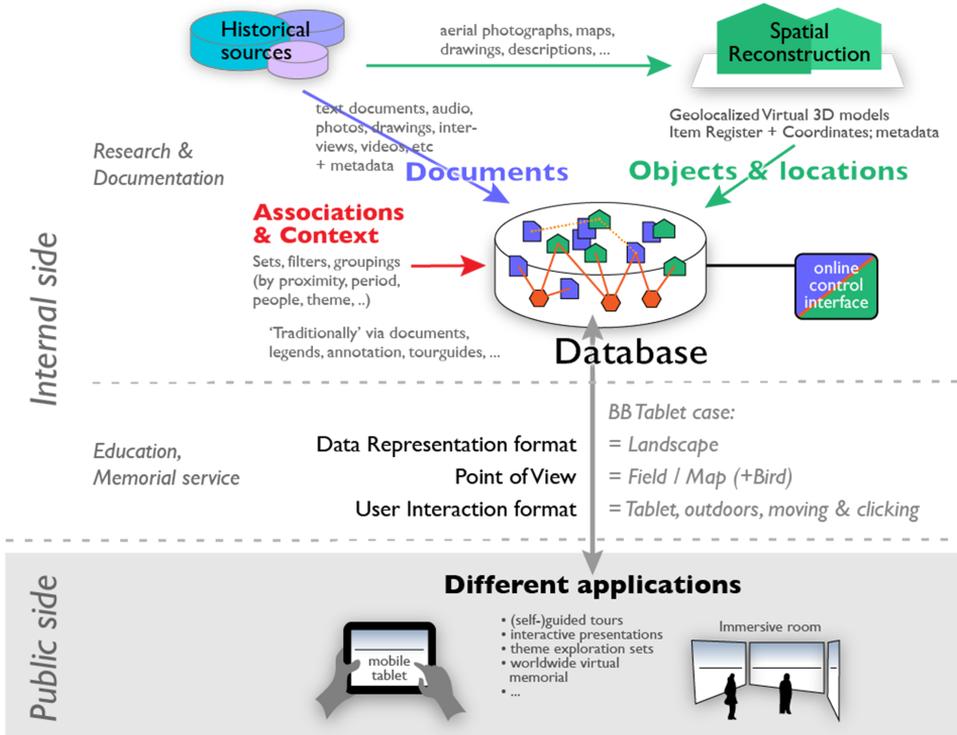


Figure 7.1: Framework Description. Main components of the framework are shown. A 3D reconstruction is used as the container of historical sources and contextual items.

7.3 Application description

7.3.1 Spatial Database

The application database constitutes an organized collection of digitized multimedia files that allows for the organization of content and its association with coordinates in the real world environment. The information stored in the database is constituted by documents and metadata-sheets, which contain multiple information fields based on the requirements of the main files. Besides hosting a corpus of content items, it also includes items that provide contextual connections between them, such as interpretative

and guiding texts (Fig. 7.1). This is particularly important for the generation of spatial narratives, one of the key components of the application.

The database structure was implemented using SQLite. To facilitate the addition and editing of content, a specific web application was developed. Edits made online in this application affect how content is displayed in the front-end (i.e., tablet application used on field). The web application includes an embedded online map implementation that allows users to simply click on a location to associate latitude and longitude coordinates to the content items.

7.3.2 Virtual Reconstruction

A second core element in this organization is a virtual, three dimensional reconstruction of an historical place, which constitutes the entrance scene to a cloud of multimedia files. Three-dimensional space is used as the container and organizer of this content: database items are deployed on top of it and can only be accessed by translating through it in the final application. The reconstruction is constituted by 3D assets that are stored in the database and have their own latitude/longitude coordinates and metadata. Besides being geolocalized, the virtual historical environment has a real world scale. In the final application, it is overlaid on top of the physical space from which it was derived using Augmented Reality — the virtual point of view being made relative to the user's position and viewing angle. The geolocalization and 1:1 mapping of the tablet application targets the generation of an immersive and physically embodied experience in the exploration of historical material in outdoor scenarios.

7.3.3 Guidance System

After content has been uploaded to the database, basic narratives can be generated by grouping specific items and controlling the sequence in which they are deployed during navigation. All this functionality can be directly accessed in the online database implementation. Points of Content (POC's) can be easily placed, edited and relocated in the physical space, and simple

groupings of them in Bundles (B), allows for the generation of both area and theme-related groups. On the other hand, basic routes can be planned by using points of presentation (PP's) — a standard feature in geolocalization / guidance systems. In our case, PP's specifically indicate real world areas from where content is visible in the final application. The differentiation between PP's and origin coordinates allows for the flexible planning of routes by taking into account the constraints of the real, physical environment and other narrative or content-related considerations.

In the first version of the architecture, two modes of navigating the data were implemented: Free, and Guided exploration. In Free mode, all PP's are made visible at the same time, and the itinerary through the data is dependent on the users' decisions. However, the content of the POC's can only be accessed when a user is near enough to the presentation point. In the Guided exploration mode, PP's are revealed stepwise forcing a predetermined trajectory through the data, with the same proximity condition applying after points became visible. This offers an important control on the users' trajectories and allows for the generation of more sophisticated narratives in the space. A preferred entry point and aiming direction were devised for each PP to suggest the user from where he should approach the content and how he should orient to the specific documents. We found this method very useful to localize photographs and aim to include height information in the metadata to automatically overlay images on top of the virtual reconstruction.

This basic system allows for the management of complex pre-scripted narratives, and includes the functionalities that are traditionally associated with audio tours. On the other hand, the system allows for an individually based, visitor-specific route guidance, given the ease and flexibility of the online database approach for the generation of sets of documents and their sequencing. Finally, the platform is prepared for the generation of interactive sequences exploiting real-time, interactive mechanisms for guidance in the near future.



Figure 7.2: Case structure for the hand-held device. An augmented view of the camp today with overlaid virtual buildings at their location in 1945.

7.3.4 Technical description

The 3D virtual reconstruction of the former camp was implemented using Autodesk Maya, 3DMax and Autocad. The interactive VR/AR application was developed in C# using the Unity3D Game Engine. Tablet computers (iPads) were chosen as hardware. Built-in GPS, compass, and gyroscope data are used as inputs to the system. GPS has a refresh rate of 200 milliseconds and an accuracy of approximately 1.5 meters. Compass data is used to recalibrate gyroscope data and align the virtual camera with the real orientation of the device with respect to cardinal points, making the orientation of the virtual space to match that of the real world. The video stream (1920x1080) of the tablet's frontal camera is combined with the digital information of the reconstruction using AR. Application is made to run in a landscape mode and iPads are covered with a graspable case for a more comfortable and safe outdoor use (Fig. 7.2).

7.4 Interaction Design

7.4.1 Interface/Interaction implementation

The tablet application supports two main view modes: “Map” and “Field” view, which correspond to a top-down and eye-height level perspective of the environment respectively. In Field Mode, Virtual and Augmented views (VR/AR) are available. Both include a virtual reconstruction of the camp in two historical states: 1944-1945. In AR mode the virtual reconstruction as well as its annotation are combined with the tablet’s camera video image of the present-day environment, providing an immersive impression of the state of the camp in 1944-1945. Both map and field view modes are available through tapping a smaller window at the bottom center of the screen (Fig. 7.3).

Information accessibility is restricted with a proximity condition (~ 10 meters) to promote physical movement through the environment. The distance of available information is informed to the users in the Map View through a circular area that surrounds their indicated position in the map. If a moving visitor brings his circle close enough to a PP icon, the content is made available.

Since the platform application is aimed at the navigation through large sets of data, large amounts of icons at various distances create cases in which the 2D layout becomes unclear. Although the map view helps identifying icon’s relative position from each other, our aim was to maximize the field view in order to promote the bodily actions of turning and translating oneself in the environment. We conceptualized a horizontal bar in which duplicate icons hover above their relative position in the perspective, which also helps to reveal content momentarily occluded by buildings. Both icons in the field and in the bar resize according to their distance to the viewer, indicating distances, and have different graphical representations to show different historical times. The top bar also provides the main access to the content: when a POC becomes available as the result of proximity, a thumbnail opens under the highlighted icon, which then can be clicked to open a fullscreen

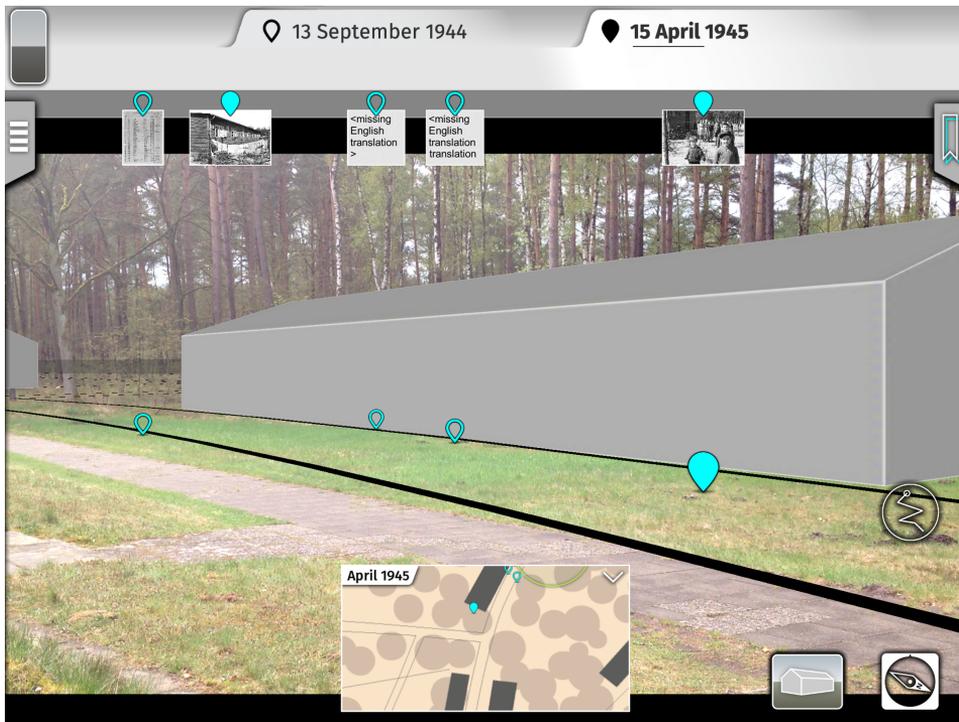


Figure 7.3: Spatial information in the Graphical User Interface. Top bar shows icons with different positions, sizes and colors indicating different content times, distances and states of availability.

content view. Once a document has been open, it can be saved into the user's list of bookmarked items and remains accessible for the rest of the session in a lateral, slidable tab (Fig. 7.3).

The top bar system was also designed to solve the problem of unreachable locations due to inaccessible parts of the environment. Typically, outdoor environments pose limitations to direct content accessibility due to trees, mud, elevations and so on. In such cases a looking direction (vector) that is associated to the PP is a good solution, and the horizontal top bar serves the purpose of directing people's gaze.

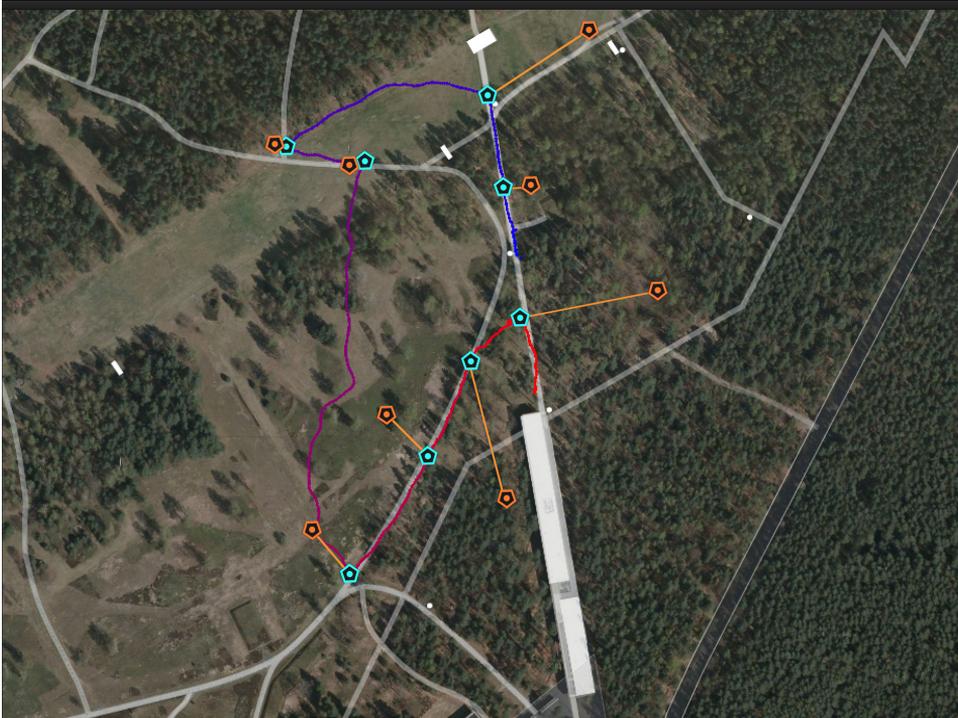


Figure 7.4: Example trajectory of a user in the Free Condition. Blue: start, red: end. Cyan and orange pentagons indicate PPs and content.

7.5 Evaluation

We aimed to get a phenomenological idea of the differences in participant’s spatial behaviour and spatial learning when experiencing Free and Guided navigation modes. We prepared sequenced and non-sequenced sets of content, and divided participants of our test study ($N=11$) in these two experimental conditions; we then asked them to move towards a particular icon’s proximity (Cyan Pentagons in Fig. 7.4) and orient themselves towards a second icon indicating a document’s position (Orange Pentagons). Users were invited to turn until they find the right orientation of the activated document, and to access content by clicking the dynamic thumbnails and markers in the top bar.

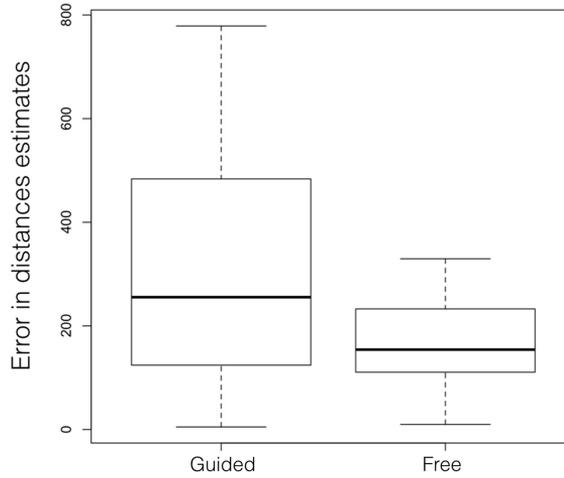


Figure 7.5: Error in allocentric distances estimates. Boxplots show distribution of errors in positioning items on a map after navigation for the Free and Guided conditions.

All of the trajectories in the guided condition ($N=5$), were similar, with subjects exactly following the paths specified by the icons. In the Free condition ($N=6$), different itineraries through the data were chosen. It must be noticed that two participants in the active condition decided to go off-road and traverse the camp in areas covered by vegetation, although all PP's were placed in the main roads of the landscape (Fig. 7.4). Both users reported to feel immersed in the augmented environment when asked about their unconventional trajectories. In general, physical movement was promoted by free exploration, suggesting that the participants were more engaged in the active condition.

To further explore the differences between the two modes of navigating the data, we asked our participants at the end of the experiment to place specific POC's previously encountered during navigation on a map of the environment. We quantified the distance between the participant's answers — i.e. where he/she placed the item on the map —, and the position where the item was encountered.

Combining results for all trials and all participants, we found a significant difference ($p < 0.01$) between the performance of the two groups in this allocentric spatial learning task, with the Free Navigation group showing less errors in allocentric distances estimates than the Guided Navigation group. Our results indicate a tendency for the participants in the Free Exploration group to show a better understanding of the spatial layout of the camp after approximately 40 mins of navigation, which is reinforced by the smaller variability in their performance (Fig. 7.5). Given the small sample size, further investigation would be required to confirm the robustness of the tendency we see in this data.

7.6 Discussion

We presented the core components of our platform, explaining the interaction design decisions we made in order to facilitate exploratory information seeking and physical navigation. We presented the results of a test study showing that participants who actively engaged in the exploration of the environment performed better in a spatial memory test compared to those who were guided in their trajectories. We believe these results might extend to a better understanding of the information digitally associated to the space (i.e. spatialized documents or sources), but further testing would be required to verify that possibility.

In the future, we would like to study how to best use the data gathered by the sensors of the devices to infer implicit user states and drive narratives. We also aim to explore the possibilities of using space to organize storytelling in the context of cultural heritage and education using different historical datasets.

Discussion

The aim of this thesis was to advance our understanding of the behavioral determinants of human long-term declarative memory and their underlying physiological substrate. A number of different research methods were employed to achieve this objective, ranging from neuropsychological testing of patients implanted with intra-cortical electrodes to the study of memory in healthy human subjects in real-world scenarios and ecologically valid experimental paradigms. We assessed memory performance and dynamics in traditional recognition and free recall memory tests and studied its neural correlates with a particular focus on the hippocampus.

Our results contribute to an interdisciplinary understanding of human memory, specifically advancing our knowledge across the disciplines of experimental psychology, neuroscience and human-computer interaction. In this last chapter, we outline the main findings presented throughout this dissertation and relate them to the current state of the art in memory research.

We started this thesis by studying the context-dependent nature of human memory with methodologies traditionally employed in the domain of spatial behavior (Chapter 2). We used Virtual Reality (VR) to build an ecologically valid space and tested participant's recognition memory for items encountered during navigation under congruent and incongruent spatial context conditions. Overcoming the limitations of traditional setups in which sub-

jects are typically not allowed to translate and items are not spatialized, our findings in this initial experiment not only confirm the high dependency of recognition memory on environmental context but also reveal a tight link between our participant's spatial behavior and their performance in the memory test. The accuracy of memory in congruent trials was higher as compared to mismatched ones, and we also found that participants who navigated more optimally in the maze also presented increased scores in the memory test. These results express the important role of human spatial learning and representation in the modulation of memory for items, and extend a long research tradition in experimental psychology that has explored spatial-context effects without considering navigational aspects (Smith and Vela, 2001).

This first study provided compelling evidence on the critical role of spatial context in modulating memory at a behavioral level, however, we aimed to characterize this contextual effect also from the perspective of the brain (Chapter 3). Theories of hippocampal function underline its critical role in the binding of spatial and sensory information; therefore, we examined the representation of context and items in the hippocampus at a physiological level. Using the unique opportunity to record activity from the brains of epileptic patients implanted with intra-cortical electrodes, we could analyze electrophysiological patterns of activity in the hippocampus while subjects performed the VR-based test described in Chapter 2. We found that congruent trials were characterized by the reinstatement of a combined representation of environmental and stimulus-derived information in the anterior hippocampus, which was locked to stimulus onset during the retrieval phase of our experiment. Moreover, we found that the hippocampus interacts with the neocortex to signal the congruency of the context of learning during the retrieval of stimulus-specific representations. Taken together, our findings in this study show that the context-dependent nature of episodic memory is mediated by the coordinated reinstatement of broadband oscillatory power in the hippocampus and the neocortex.

Grounded on our initial results, we hypothesized that spatial context and

behavior would affect not only memory performance but also its long-term *structure* (Chapter 4). Inspired by spatial mnemonics such as the method of Loci, which deploy the brain's spatial representational system to organize items that are not necessarily spatial by their nature, we evaluated the influence of space in defining the associative structure of stimuli in memory. It has been argued that the study of free recall dynamics is instrumental in characterizing the organizational structure of human memory (Kahana, 2012). Previous research has shown that space plays a key role in defining such structure. Our results confirmed a tendency for participants to contiguously recall items presented close by during navigation as previously reported. Critically, we observed the same effect in a test conducted 24 hours after learning, suggesting a long-term stability of the spatial structure. In addition, we found that the clustering of items in the delayed test was systematically related to mnemonic performance at that time point. While other studies have reported spatial clustering effects in immediate or shortly delayed tests, our results are the first to highlight their long-term stability, underlining the tight relationship of SCs with mnemonic performance and forgetting. Taken together, our results in this second behavioral experiment reveal a firm modulation of the associative structure of memory by spatial factors, even when participants were not instructed to memorize the locations of the items or to use them as cues to guide recall.

Throughout this dissertation, and in addition to the role of context in determining memory accuracy and structure, we have presented evidence of the role of human agency in the modulation of mnemonic performance from two behavioral and one neurophysiological study. In the first behavioral paradigm (Chapter 4), we investigated how action affects the structure of memory by assessing free recall dynamics of items encoded under active and passive navigation conditions. Participants could freely decide on the routes to take during navigation to reach specific items or were passively exposed to the trajectory of another subject. Results revealed a lack of significant differences in recall performance nor spatial clustering scores across the two groups of participants. As discussed in the conclusions of Chapter 4, these

somehow unexpected results might be related to the operationalization of the “free” condition in this particular setup, which did not involve the control over the sequential order of study of the items to be learned. These null results, however, should not be taken as definitive evidence on the role of agency in the structuring of items in memory. Indeed, it is relevant to address in future research the role of self-directed learning on spatial clustering when timings and materials of study are in the control of the learner. A second important issue that deserves further investigation relates to the role of physical movement in the clustering scores, given the prominent role assigned to this factor in the formation of memory boundaries (Zacks et al., 2007).

In a second “active learning” paradigm, we let subjects control data exploration i.e., navigation and access to items, including timings and materials of study on a moment by moment basis (Chapter 5). We assessed whether recognition memory for those items would be modulated by the level of control over the learning process, following a yoked experimental design. Our results revealed that volitional knowledge acquisition positively modulates memory, as reflected in the increased recognition accuracy for volitional as opposed to passive learning conditions. In line with the literature, we found this effect to be more pronounced in items studied for longer periods of time.

To explore the correlates of the observed effect in the brain, we conducted the same active learning protocol in a group of six patients implanted with intracortical electrodes. We specifically targeted the hippocampus, given its well-established role in coordinating voluntary behaviors and active information sampling expressed in the animal literature. We found prominent differences in oscillatory activity between self-directed and passive learning conditions. Active learning was characterized by increased oscillatory power in the theta (2-7Hz) band as compared to passive memorization. Our findings in this neurophysiological study show, to our knowledge for the first time, a link of active learning and hippocampal theta oscillations in humans, extending previous human fMRI studies which have first characterized the involvement of the hippocampus in the process (Voss et al., 2011a).

Finally, in the last two chapters of this dissertation, we have presented a novel educational tool for human-data interaction in educational contexts, which is grounded in the principles of active data exploration and context-dependent memory previously discussed. We have shown that space can be used to orchestrate the interaction with digital content capitalizing on novel Information and Communication Technologies (ITC). We have particularly described the technical implementation of a hand-held Augmented Reality (AR) application that promotes the active and spatial exploration of documents in outdoor scenarios. As opposed to traditional information seeking models which tend to understand human information behavior in disembodied terms, our paradigm uses the notion of space as an anchor of information and meaning. Preliminary feedback from users in the Bergen-Belsen memorial suggests that integrating the principles of active navigation and embodied spatial exploration — by facilitating, for instance, the generation of spatialized narratives —, can lead to more profound and engaging learning experiences.

In addition to the relevance of understanding the nature of memory to fundamental scientific research, it is of great value to society to understand how memory works. Knowledge of memory can lead us to improve educational practices and design better learning technologies. Understanding the neural mechanisms of memory can help us to improve diagnose tools and eventually cure diseases associated with memory loss. This thesis work advances our understanding of memory from a behavioral and neurophysiological perspective, highlighting the relevance of this knowledge in the design of future educational paradigms.

Bibliography

Each reference indicates the pages where it appears.

- C. Aart, B. Wielinga, and W. Hage. Mobile cultural heritage guide: Location-aware semantic search. In P. Cimiano and H. Pinto, editors, *Knowledge Engineering and Management by the Masses*, volume 6317 of *Lecture Notes in Computer Science*, pages 257–271. Springer Berlin Heidelberg, 2010. ISBN 978-3-642-16437-8. doi: 10.1007/978-3-642-16438-5_18. URL http://dx.doi.org/10.1007/978-3-642-16438-5_18.
- E. Ackermann. Perspective-taking and object construction: Two keys to learning. *Constructionism in practice: designing, thinking, and learning in a digital world*, Lawrence Erlbaum, Mahwah, NJ, pages 25–35, 1996.
- G. Agarwal, I. H. Stevenson, A. Berényi, K. Mizuseki, G. Buzsáki, and F. T. Sommer. Spatially distributed local fields in the hippocampus encode rat position. *Science*, 344(6184):626–630, 2014.
- J. P. Aggleton and M. W. Brown. Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behavioral and Brain Sciences*, 22(3):425–444, 1999.
- Z. M. Aghajian, P. Schuette, T. Fields, M. Tran, S. Siddiqui, N. Hasulak, T. K. Tcheng, D. Eliashiv, J. Stern, I. Fried, et al. Theta oscillations in

- the human medial temporal lobe during real world ambulatory movement. *bioRxiv*, page 078055, 2016.
- P. Alvarez and L. R. Squire. Memory consolidation and the medial temporal lobe: a simple network model. *Proceedings of the National Academy of Sciences*, 91(15):7041–7045, 1994.
- J. Annese, N. M. Schenker-Ahmed, H. Bartsch, P. Maechler, C. Sheh, N. Thomas, J. Kayano, A. Ghatan, N. Bresler, M. P. Frosch, et al. Post-mortem examination of patient hm’s brain based on histological sectioning and digital 3d reconstruction. *Nature communications*, 5, 2014.
- D. Aronov, R. Nevers, and D. W. Tank. Mapping of a non-spatial dimension by the hippocampal–entorhinal circuit. *Nature*, 543(7647):719–722, 2017.
- R. C. Atkinson and R. M. Shiffrin. Human memory: A proposed system and its control processes. *The psychology of learning and motivation*, 2: 89–195, 1968.
- N. M. Avouris and N. Yiannoutsou. A review of mobile location-based games for learning across physical and virtual spaces. *J. UCS*, 18(15):2120–2142, 2012.
- A. Baddeley. Working memory. *Science*, 255(5044):556–559, 1992. ISSN 0036-8075. doi: 10.1126/science.1736359. URL <http://science.sciencemag.org/content/255/5044/556>.
- A. Baddeley. Working memory: looking back and looking forward. *Nature Reviews. Neuroscience*, 4(10):829, 2003.
- A. D. Baddeley and G. Hitch. Working memory. *Psychology of learning and motivation*, 8:47–89, 1974.
- M. J. Bates. The design of browsing and berrypicking techniques for the online search interface. *Online Information Review*, 13(5):407–424, 1989.
- R. W. Berg, D. Whitmer, and D. Kleinfeld. Exploratory whisking by rat is not phase locked to the hippocampal theta rhythm. *Journal of Neuroscience*, 26(24):6518–6522, 2006.
- H. Berger. Über das elektrenkephalogramm des menschen. *European Archives of Psychiatry and Clinical Neuroscience*, 87(1):527–570, 1929.

- A. Berndt, S. Y. Lee, J. Wietek, C. Ramakrishnan, E. E. Steinberg, A. J. Rashid, H. Kim, S. Park, A. Santoro, P. W. Frankland, et al. Structural foundations of optogenetics: Determinants of channelrhodopsin ion selectivity. *Proceedings of the National Academy of Sciences*, 113(4):822–829, 2016.
- S. D. Berry and R. F. Thompson. Prediction of learning rate from the hippocampal electroencephalogram. *Science*, 200(4347):1298–1300, 1978.
- A. Betella, E. M. Bueno, U. Bernardet, and P. F. Verschure. The effect of guided and free navigation on spatial memory in mixed reality. In *Proceedings of the Virtual Reality International Conference: Laval Virtual*, page 7. ACM, 2013.
- C. M. Bird and N. Burgess. The hippocampus and memory: insights from spatial processing. *Nature Reviews Neuroscience*, 9(3):182–194, 2008.
- C. M. Bird, J. A. Bisby, and N. Burgess. The hippocampus and spatial constraints on mental imagery. *Frontiers in human neuroscience*, 6:142, 2012.
- V. D. Bohbot, M. S. Copara, J. Gotman, and A. D. Ekstrom. Low-frequency theta oscillations in the human hippocampus during real-world and virtual navigation. *Nature Communications*, 8:14415, 2017.
- E. Bostock, R. U. Muller, and J. L. Kubie. Experience-dependent modifications of hippocampal place cell firing. *Hippocampus*, 1(2):193–205, 1991.
- G. H. Bower. Analysis of a mnemonic device: Modern psychology uncovers the powerful components of an ancient system for improving memory. *American Scientist*, 58(5):496–510, 1970.
- M. A. B. Brazier. *The historical development of neurophysiology*. American Physiological Society, 1959.
- T. I. Brown, V. A. Carr, K. F. LaRocque, S. E. Favila, A. M. Gordon, B. Bowles, J. N. Bailenson, and A. D. Wagner. Prospective representation of navigational goals in the human hippocampus. *Science*, 352(6291):1323–1326, 2016.

- J. S. Bruner. The act of discovery. *Harvard educational review*, 1961.
- M. Bunsey and H. Eichenbaum. Conservation of hippocampal memory function in rats and humans. *Nature*, 379(6562):255, 1996.
- N. Burgess, E. A. Maguire, and J. O'Keefe. The human hippocampus and spatial and episodic memory. *Neuron*, 35(4):625–641, 2002.
- J. F. Burke, A. D. Sharan, M. R. Sperling, A. G. Ramayya, J. J. Evans, M. K. Healey, E. N. Beck, K. A. Davis, T. H. Lucas, and M. J. Kahana. Theta and high-frequency activity mark spontaneous recall of episodic memories. *Journal of Neuroscience*, 34(34):11355–11365, 2014.
- G. Buzsáki. Long-term changes of hippocampal sharp-waves following high frequency afferent activation. *Brain research*, 300(1):179–182, 1984.
- G. Buzsáki. Theta oscillations in the hippocampus. *Neuron*, 33(3):325–340, 2002.
- G. Buzsáki. Theta rhythm of navigation: link between path integration and landmark navigation, episodic and semantic memory. *Hippocampus*, 15(7):827–840, 2005.
- G. Buzsáki. *Rhythms of the Brain*. Oxford University Press, 2006.
- G. Buzsáki. Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. *Hippocampus*, 25(10):1073–1188, 2015.
- G. Buzsáki and E. I. Moser. Memory, navigation and theta rhythm in the hippocampal-entorhinal system. *Nature neuroscience*, 16(2):130–138, 2013.
- G. Buzsáki, A. Bragin, J. Chrobak, Z. Nadasdy, A. Sik, M. Hsu, and A. Ylinen. Oscillatory and intermittent synchrony in the hippocampus: relevance to memory trace formation. In *Temporal coding in the brain*, pages 145–172. Springer, 1994.
- G. Buzsáki, C. A. Anastassiou, and C. Koch. The origin of extracellular fields and currents—eeg, ecog, lfp and spikes. *Nature reviews neuroscience*, 13(6):407–420, 2012.
- D. Callebaut and J. Sunderland. Ename: new technologies perpetuate the past. *Museum International*, 50(2):50–54, 1998.

- K. A. Cameron, S. Yashar, C. L. Wilson, and I. Fried. Human hippocampal neurons predict how well word pairs will be remembered. *Neuron*, 30(1): 289–298, 2001.
- A. Carassa, G. Geminiani, F. Morganti, and D. Varotto. Active and passive spatial learning in a complex virtual environment: The effect of efficient exploration. *Cognitive processing*, 3(4):65–81, 2002.
- M. F. Carr, S. P. Jadhav, and L. M. Frank. Hippocampal replay in the awake state: a potential substrate for memory consolidation and retrieval. *Nature neuroscience*, 14(2):147–153, 2011.
- G. Chen, J. A. King, N. Burgess, and J. O’Keefe. How vision and movement combine in the hippocampal place code. *Proceedings of the National Academy of Sciences*, 110(1):378–383, 2013.
- E. R. Chrastil. Neural evidence supports a novel framework for spatial navigation. *Psychonomic bulletin & review*, 20(2):208–27, 2013. ISSN 1531-5320. doi: 10.3758/s13423-012-0351-6. URL <http://www.ncbi.nlm.nih.gov/pubmed/23229443>.
- E. R. Chrastil and W. H. Warren. Active and passive contributions to spatial learning. *Psychonomic bulletin & review*, 19(1):1–23, 2012.
- C. G. Christou and H. H. Bühlhoff. View dependence in scene recognition after active learning. *Memory & Cognition*, 27(6):996–1007, 1999.
- N. J. Cohen, L. R. Squire, et al. Preserved learning and retention of pattern-analyzing skill in amnesia: Dissociation of knowing how and knowing that. *Science*, 210(4466):207–210, 1980.
- N. J. Cohen, R. A. Poldrack, and H. Eichenbaum. Memory for items and memory for relations in the procedural/declarative memory framework. *Memory*, 5(1-2):131–178, 1997.
- L. L. Colgin. Rhythms of the hippocampal network. *Nature reviews. Neuroscience*, 17(4):239, 2016.
- L. L. Colgin, E. I. Moser, and M.-B. Moser. Understanding memory through hippocampal remapping. *Trends in neurosciences*, 31(9):469–477, 2008.

- A. M. Collins and M. R. Quillian. Retrieval time from semantic memory. *Journal of verbal learning and verbal behavior*, 8(2):240–247, 1969.
- C. Concordia, S. Gradmann, and S. Siebinga. Not just another portal, not just another digital library: A portrait of europeana as an application program interface. *IFLA Journal*, 36(1):61–69, 2010. doi: 10.1177/0340035209360764. URL <http://ifl.sagepub.com/content/36/1/61.abstract>.
- E. Corder, A. Saunders, W. Strittmatter, D. Schmechel, P. Gaskell, G. a. Small, A. Roses, J. Haines, and M. A. Pericak-Vance. Gene dose of apolipoprotein e type 4 allele and the risk of alzheimer’s disease in late onset families. *Science*, 261(5123):921–923, 1993.
- S. Corkin. Lasting consequences of bilateral medial temporal lobectomy: Clinical course and experimental findings in hm. In *Seminars in Neurology*, volume 4, pages 249–259. © 1984 by Thieme Medical Publishers, Inc., 1984.
- S. Corkin. *Permanent present tense: The unforgettable life of the amnesic patient, HM*, volume 1000. Basic Books (AZ), 2013.
- N. R. Council et al. *How people learn: Bridging research and practice*. National Academies Press, 1999.
- K. K. Cowansage, T. Shuman, B. C. Dillingham, A. Chang, P. Golshani, and M. Mayford. Direct reactivation of a coherent neocortical memory of context. *Neuron*, 84(2):432–441, 2014.
- L. Davachi. Item, context and relational episodic encoding in humans. *Current opinion in neurobiology*, 16(6):693–700, 2006.
- A. J. Dede, J. T. Wixted, R. O. Hopkins, and L. R. Squire. Hippocampal damage impairs recognition memory broadly, affecting both parameters in two prominent models of memory. *Proceedings of the National Academy of Sciences*, 110(16):6577–6582, 2013.
- A. J. Dede, J. C. Frascino, J. T. Wixted, and L. R. Squire. Learning and remembering real-world events after medial temporal lobe damage. *Proceedings of the National Academy of Sciences*, 113(47):13480–13485, 2016a.

- A. J. Dede, J. T. Wixted, R. O. Hopkins, and L. R. Squire. Autobiographical memory, future imagining, and the medial temporal lobe. *Proceedings of the National Academy of Sciences*, 113(47):13474–13479, 2016b.
- J. DeFelipe. Brain plasticity and mental processes: Cajal again. *Nature reviews. Neuroscience*, 7(10):811, 2006.
- A. Delorme and S. Makeig. Eeglab: an open source toolbox for analysis of single-trial eeg dynamics including independent component analysis. *Journal of neuroscience methods*, 134(1):9–21, 2004.
- C. A. Denny, M. A. Kheirbek, E. L. Alba, K. F. Tanaka, R. A. Brachman, K. B. Laughman, N. K. Tomm, G. F. Turi, A. Losonczy, and R. Hen. Hippocampal memory traces are differentially modulated by experience, time, and adult neurogenesis. *Neuron*, 83(1):189–201, 2014.
- D. Derdikman and E. I. Moser. A manifold of spatial maps in the brain. *Trends in cognitive sciences*, 14(12):561–569, 2010.
- C. F. Doeller, C. Barry, and N. Burgess. Evidence for grid cells in a human memory network. *Nature*, 463(7281):657–661, 2010.
- G. Dragoi and S. Tonegawa. Preplay of future place cell sequences by hippocampal cellular assemblies. *Nature*, 469(7330):397, 2011.
- G. Dragoi and S. Tonegawa. Distinct preplay of multiple novel spatial experiences in the rat. *Proceedings of the National Academy of Sciences*, 110(22):9100–9105, 2013.
- M. J. Eacott, A. Easton, and A. Zinkivskay. Recollection in an episodic-like memory task in the rat. *Learning & Memory*, 12(3):221–223, 2005.
- H. Eichenbaum. *Memory, amnesia, and the hippocampal system*. MIT press, 1993.
- H. Eichenbaum. Hippocampus: cognitive processes and neural representations that underlie declarative memory. *Neuron*, 44(1):109–120, 2004.
- H. Eichenbaum. What hm taught us. *Journal of cognitive neuroscience*, 25(1):14–21, 2013.
- H. Eichenbaum. Time cells in the hippocampus: a new dimension for mapping memories. *Nature Reviews Neuroscience*, 15(11):732–744, 2014.

- H. Eichenbaum. On the integration of space, time, and memory. *Neuron*, 95(5):1007–1018, 2017.
- H. Eichenbaum and N. J. Cohen. *From conditioning to conscious recollection: Memory systems of the brain*. Number 35. Oxford University Press on Demand, 2004.
- H. Eichenbaum and N. J. Cohen. Can we reconcile the declarative memory and spatial navigation views on hippocampal function? *Neuron*, 83(4):764–770, 2014.
- H. Eichenbaum, P. Dudchenko, E. Wood, M. Shapiro, and H. Tanila. The hippocampus, memory, and place cells: is it spatial memory or a memory space? *Neuron*, 23(2):209–226, 1999.
- H. Eichenbaum, A. P. Yonelinas, and C. Ranganath. The medial temporal lobe and recognition memory. *Annu. Rev. Neurosci.*, 30:123–152, 2007.
- H. Eichenbaum, M. Sauvage, N. Fortin, R. Komorowski, and P. Lipton. Towards a functional organization of episodic memory in the medial temporal lobe. *Neuroscience & Biobehavioral Reviews*, 36(7):1597–1608, 2012.
- A. Ekstrom, I. Viskontas, M. Kahana, J. Jacobs, K. Upchurch, S. Bookheimer, and I. Fried. Contrasting roles of neural firing rate and local field potentials in human memory. *Hippocampus*, 17(8):606–617, 2007.
- A. D. Ekstrom and C. Ranganath. Space, time and episodic memory: the hippocampus is all over the cognitive map. *Hippocampus*, 2017.
- A. D. Ekstrom and A. J. Watrous. Multifaceted roles for low-frequency oscillations in bottom-up and top-down processing during navigation and memory. *Neuroimage*, 85:667–677, 2014.
- A. D. Ekstrom, M. J. Kahana, J. B. Caplan, T. A. Fields, et al. Cellular networks underlying human spatial navigation. *Nature*, 425(6954):184, 2003.
- A. D. Ekstrom, J. B. Caplan, E. Ho, K. Shattuck, I. Fried, and M. J. Kahana. Human hippocampal theta activity during virtual navigation. *Hippocampus*, 15(7):881–889, 2005.

- Y. Ezzyat and L. Davachi. What constitutes an episode in episodic memory? *Psychological Science*, 22(2):243–252, 2011.
- J. Fell, P. Klaver, K. Lehnertz, T. Grunwald, C. Schaller, C. E. Elger, and G. Fernández. Human memory formation is accompanied by rhinal–hippocampal coupling and decoupling. *Nature neuroscience*, 4(12):1259–1264, 2001.
- J. Fell, E. Ludowig, B. P. Staresina, T. Wagner, T. Kranz, C. E. Elger, and N. Axmacher. Medial temporal theta/alpha power enhancement precedes successful memory encoding: evidence based on intracranial eeg. *Journal of Neuroscience*, 31(14):5392–5397, 2011.
- A. Fernandez and A. M. Glenberg. Changing environmental context does not reliably affect memory. *Memory & Cognition*, 13(4):333–345, 1985.
- J. Foer. *Moonwalking with Einstein: The art and science of remembering everything*. Penguin, 2011.
- D. J. Foster and M. A. Wilson. Reverse replay of behavioural sequences in hippocampal place cells during the awake state. *Nature*, 440(7084):680–683, 2006.
- I. Fried, K. A. MacDonald, and C. L. Wilson. Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron*, 18(5):753–765, 1997.
- M. Fyhn, T. Hafting, A. Treves, M.-B. Moser, and E. I. Moser. Hippocampal remapping and grid realignment in entorhinal cortex. *Nature*, 446(7132):190–194, 2007.
- F. Gaunet, M. Vidal, A. Kemeny, and A. Berthoz. Active, passive and snapshot exploration in a virtual environment: influence on scene memory, reorientation and path memory. *Cognitive Brain Research*, 11(3):409–420, 2001.
- R. E. Geiselman and R. A. Bjork. Primary versus secondary rehearsal in imagined voices: Differential effects on recognition. *Cognitive Psychology*, 12(2):188–205, 1980.
- R. E. Geiselman and J. Glenny. Effects of imagining speakers’ voices on the

- retention of words presented visually. *Memory & Cognition*, 5(5):499–504, 1977.
- H. Gelbard-Sagiv, R. Mukamel, M. Harel, R. Malach, and I. Fried. Internally generated reactivation of single neurons in human hippocampus during free recall. *Science*, 322(5898):96–101, 2008.
- J. J. Gibson. *The ecological approach to visual perception: classic edition*. Psychology Press, 2014.
- L. M. Giocomo, M.-B. Moser, and E. I. Moser. Computational models of grid cells. *Neuron*, 71(4):589–603, 2011.
- D. Godden and A. Baddeley. When does context influence recognition memory? *British journal of Psychology*, 71(1):99–104, 1980.
- D. R. Godden and A. D. Baddeley. Context-dependent memory in two natural environments: On land and underwater. *British Journal of psychology*, 66(3):325–331, 1975.
- D. S. Gorfein and R. R. Hoffman. *Memory and learning: The Ebbinghaus centennial conference*. Lawrence Erlbaum, 1987.
- S. C. Grant and L. E. Magee. Contributions of proprioception to navigation in virtual environments. *Human Factors: The Journal of the Human Factors and Ergonomics Society*, 40(3):489–497, 1998.
- S. Guderian, B. H. Schott, A. Richardson-Klavehn, and E. Düzel. Medial temporal theta state before an event predicts episodic encoding success in humans. *Proceedings of the National Academy of Sciences*, 106(13):5365–5370, 2009.
- A. S. Gupta, M. A. van der Meer, D. S. Touretzky, and A. D. Redish. Hippocampal replay is not a simple function of experience. *Neuron*, 65(5):695–705, 2010.
- T. M. Gureckis and D. B. Markant. Self-directed learning: A cognitive and computational perspective. *Perspectives on Psychological Science*, 7(5):464–481, 2012.
- R. Hable, T. Rößler, and C. Schuller. evoguide: implementation of a tour guide support solution with multimedia and augmented-reality content.

- In *Proceedings of the 11th International Conference on Mobile and Ubiquitous Multimedia*, page 29. ACM, 2012.
- T. Hafting, M. Fyhn, S. Molden, M.-B. Moser, and E. I. Moser. Microstructure of a spatial map in the entorhinal cortex. *Nature*, 436(7052):801–806, 2005.
- J.-H. Han, S. A. Kushner, A. P. Yiu, H.-L. L. Hsiang, T. Buch, A. Waisman, B. Bontempi, R. L. Neve, P. W. Frankland, and S. A. Josselyn. Selective erasure of a fear memory. *Science*, 323(5920):1492–1496, 2009.
- O. Hardt, K. Nader, and L. Nadel. Decay happens: the role of active forgetting in memory. *Trends in cognitive sciences*, 17(3):111–120, 2013.
- A. L. Haskins, A. P. Yonelinas, J. R. Quamme, and C. Ranganath. Perirhinal cortex supports encoding and familiarity-based recognition of novel associations. *Neuron*, 59(4):554–560, 2008.
- D. Hassabis, D. Kumaran, S. D. Vann, and E. A. Maguire. Patients with hippocampal amnesia cannot imagine new experiences. *Proceedings of the National Academy of Sciences*, 104(5):1726–1731, 2007.
- D. Hassabis, C. Chu, G. Rees, N. Weiskopf, P. D. Molyneux, and E. A. Maguire. Decoding neuronal ensembles in the human hippocampus. *Current Biology*, 19(7):546–554, 2009.
- M. E. Hasselmo, C. Bodelón, and B. P. Wyble. A proposed function for hippocampal theta rhythm: separate phases of encoding and retrieval enhance reversal of prior learning. *Neural computation*, 14(4):793–817, 2002.
- J. V. Haxby, M. I. Gobbini, M. L. Furey, A. Ishai, J. L. Schouten, and P. Pietrini. Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science*, 293(5539):2425–2430, 2001.
- D. Hebb. *The organisation of behavior* wiley. *New York*, 1949.
- K. Henke. A model for memory systems based on processing modes rather than consciousness. *Nature reviews. Neuroscience*, 11(7):523, 2010.
- W. E. Hockley. The effects of environmental context on recognition memory

- and claims of remembering. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 34(6):1412, 2008.
- K. Hoffman and B. McNaughton. Coordinated reactivation of distributed memory traces in primate neocortex. *Science*, 297(5589):2070–2073, 2002.
- J. J. Hopfield. Neural networks and physical systems with emergent collective computational abilities. *Proceedings of the national academy of sciences*, 79(8):2554–2558, 1982.
- A. J. Horner and N. Burgess. Pattern completion in multielement event engrams. *Current Biology*, 24(9):988–992, 2014.
- A. J. Horner, J. A. Bisby, A. Wang, K. Bogus, and N. Burgess. The role of spatial boundaries in shaping long-term event representations. *Cognition*, 154:151–164, 2016.
- M. W. Howard and M. J. Kahana. Contextual variability and serial position effects in free recall. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 25(4):923, 1999.
- M. W. Howard and M. J. Kahana. A distributed representation of temporal context. *Journal of Mathematical Psychology*, 46(3):269–299, 2002.
- H.-L. L. Hsiang, J. R. Epp, M. C. van den Oever, C. Yan, A. J. Rashid, N. Insel, L. Ye, Y. Niibori, K. Deisseroth, P. W. Frankland, et al. Manipulating a “cocaine engram” in mice. *Journal of Neuroscience*, 34(42):14115–14127, 2014.
- M. Hübener and T. Bonhoeffer. Searching for engrams. *Neuron*, 67(3):363–371, 2010.
- P. T. Huerta and J. E. Lisman. Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in ca1 in vitro. *Neuron*, 15(5):1053–1063, 1995.
- R. S. R. T. Hummel, J. Quellen zur topografie bergens-belsen 1938 - 1945. Stiftung niedersächsische Gedenkstätten Gedenkstätte Bergen-Belsen, 2008.
- A. Hupbach, O. Hardt, R. Gomez, and L. Nadel. The dynamics of memory: Context-dependent updating. *Learning & Memory*, 15(8):574–579, 2008.

- J. Jacobs. Hippocampal theta oscillations are slower in humans than in rodents: implications for models of spatial navigation and memory. *Phil. Trans. R. Soc. B*, 369(1635):20130304, 2014.
- J. Jacobs and M. J. Kahana. Direct brain recordings fuel advances in cognitive electrophysiology. *Trends in cognitive sciences*, 14(4):162–171, 2010.
- J. Jacobs, C. T. Weidemann, J. F. Miller, A. Solway, J. F. Burke, X.-X. Wei, N. Suthana, M. R. Sperling, A. D. Sharan, I. Fried, et al. Direct recordings of grid-like neuronal activity in human spatial navigation. *Nature neuroscience*, 16(9):1188–1190, 2013.
- W. James. The principles of psychology. 2 vols. new york: Henry holt and company, 1890.
- A. I. Jang, J. H. Wittig, S. K. Inati, and K. A. Zaghloul. Human cortical neurons in the anterior temporal lobe reinstate spiking activity during verbal memory retrieval. *Current Biology*, 2017.
- D. Ji and M. A. Wilson. Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nature neuroscience*, 10(1):100, 2007.
- E. L. Johnson and R. T. Knight. Intracranial recordings and human memory. *Current opinion in neurobiology*, 31:18–25, 2015.
- S. A. Josselyn, S. Köhler, and P. W. Frankland. Finding the engram. *Nature reviews. Neuroscience*, 16(9):521, 2015.
- M. J. Jutras, P. Fries, and E. A. Buffalo. Gamma-band synchronization in the macaque hippocampus and memory formation. *Journal of Neuroscience*, 29(40):12521–12531, 2009.
- M. J. Kahana. *Foundations of human memory*. Oxford University Press, 2012.
- J. Keil, M. Zoellner, T. Engelke, F. Wientapper, and M. Schmitt. Controlling and filtering information density with spatial interaction techniques via handheld augmented reality. In *Virtual augmented and mixed reality. Designing and developing augmented and virtual environments*, pages 49–57. Springer, 2013.
- T. Kitamura, S. K. Ogawa, D. S. Roy, T. Okuyama, M. D. Morrissey, L. M.

- Smith, R. L. Redondo, and S. Tonegawa. Engrams and circuits crucial for systems consolidation of a memory. *Science*, 356(6333):73–78, 2017.
- K. A. Klein, K. M. Addis, and M. J. Kahana. A comparative analysis of serial and free recall. *Memory & Cognition*, 33(5):833–839, 2005.
- D. Kolb. Experiential education: Experience as the source of learning and development. *Englewood Cliffs, NJ*, 1984.
- D. Koller, B. Frischer, and G. Humphreys. Research challenges for digital archives of 3d cultural heritage models. *journal on computing and cultural heritage (JOCCH)*, 2(3):7, 2009.
- A. Konkel and N. J. Cohen. Relational memory and the hippocampus: representations and methods. *Frontiers in Neuroscience*, 3(2):166, 2009.
- N. Kornell and J. Metcalfe. Study efficacy and the region of proximal learning framework. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 32(3):609, 2006.
- A. Kraskov, R. Q. Quiroga, L. Reddy, I. Fried, and C. Koch. Local field potentials and spikes in the human medial temporal lobe are selective to image category. *Journal of cognitive neuroscience*, 19(3):479–492, 2007.
- B. J. Kraus, R. J. Robinson, J. A. White, H. Eichenbaum, and M. E. Hasselmo. Hippocampal “time cells”: time versus path integration. *Neuron*, 78(6):1090–1101, 2013.
- G. Kreiman, C. Koch, and I. Fried. Category-specific visual responses of single neurons in the human medial temporal lobe. *Nature neuroscience*, 3(9):946, 2000a.
- G. Kreiman, C. Koch, and I. Fried. Imagery neurons in the human brain. *Nature*, 408(6810):357, 2000b.
- N. Kriegeskorte, M. Mur, and P. Bandettini. Representational similarity analysis—connecting the branches of systems neuroscience. *Frontiers in systems neuroscience*, 2, 2008.
- E. Kropff, J. E. Carmichael, M.-B. Moser, and E. I. Moser. Speed cells in the medial entorhinal cortex. *Nature*, 523(7561):419–424, 2015.
- L. Kunz, T. N. Schröder, H. Lee, C. Montag, B. Lachmann, R. Sariyska,

- M. Reuter, R. Stirnberg, T. Stöcker, P. C. Messing-Floeter, et al. Reduced grid-cell-like representations in adults at genetic risk for alzheimer's disease. *Science*, 350(6259):430–433, 2015.
- C.-F. V. Latchoumane, H.-V. V. Ngo, J. Born, and H.-S. Shin. Thalamic spindles promote memory formation during sleep through triple phase-locking of cortical, thalamic, and hippocampal rhythms. *Neuron*, 95(2):424–435, 2017.
- H. A. Lechner, L. R. Squire, and J. H. Byrne. 100 years of consolidation—remembering müller and pilzecker. *Learning & Memory*, 6(2):77–87, 1999.
- A. K. Lee and M. A. Wilson. Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron*, 36(6):1183–1194, 2002.
- H. Lee, J. Fell, and N. Axmacher. Electrical engram: how deep brain stimulation affects memory. *Trends in cognitive sciences*, 17(11):574–584, 2013.
- B. C. Lega, J. Jacobs, and M. Kahana. Human hippocampal theta oscillations and the formation of episodic memories. *Hippocampus*, 22(4):748–761, 2012.
- J. K. Leutgeb, S. Leutgeb, M.-B. Moser, and E. I. Moser. Pattern separation in the dentate gyrus and ca3 of the hippocampus. *science*, 315(5814):961–966, 2007.
- S. Leutgeb and J. K. Leutgeb. Pattern separation, pattern completion, and new neuronal codes within a continuous ca3 map. *Learning & memory*, 14(11):745–757, 2007.
- S. Leutgeb, J. K. Leutgeb, C. A. Barnes, E. I. Moser, B. L. McNaughton, and M.-B. Moser. Independent codes for spatial and episodic memory in hippocampal neuronal ensembles. *Science*, 309(5734):619–623, 2005.
- J. Lisman. The challenge of understanding the brain: Where we stand in 2015. *Neuron*, 86(4):864–882, 2015.
- J. E. Lisman and M. A. Idiart. Storage of 7 plus/minus 2 short-term memories in oscillatory subcycles. *Science*, 267(5203):1512, 1995.
- J. E. Lisman and O. Jensen. The theta-gamma neural code. *Neuron*, 77(6):1002–1016, 2013.

- X. Liu, S. Ramirez, P. T. Pang, C. B. Puryear, A. Govindarajan, K. Deisseroth, and S. Tonegawa. Optogenetic stimulation of a hippocampal engram activates fear memory recall. *Nature*, 484(7394):381–385, 2012.
- N. M. Long, J. F. Burke, and M. J. Kahana. Subsequent memory effect in intracranial and scalp eeg. *Neuroimage*, 84:488–494, 2014.
- L. Lu, J. K. Leutgeb, A. Tsao, E. J. Henriksen, S. Leutgeb, C. A. Barnes, M. P. Witter, M.-B. Moser, and E. I. Moser. Impaired hippocampal rate coding after lesions of the lateral entorhinal cortex. *Nature neuroscience*, 16(8):1085–1093, 2013.
- S. J. Luck. *An introduction to the event-related potential technique*. MIT press, 2014.
- W. J. Ma, M. Husain, and P. M. Bays. Changing concepts of working memory. *Nature neuroscience*, 17(3):347–356, 2014.
- C. J. MacDonald, K. Q. Lepage, U. T. Eden, and H. Eichenbaum. Hippocampal “time cells” bridge the gap in memory for discontinuous events. *Neuron*, 71(4):737–749, 2011.
- F. Macrides, H. B. Eichenbaum, and W. B. Forbes. Temporal relationship between sniffing and the limbic theta rhythm during odor discrimination reversal learning. *Journal of Neuroscience*, 2(12):1705–1717, 1982.
- E. A. Maguire and S. L. Mullally. The hippocampus: a manifesto for change. *Journal of Experimental Psychology: General*, 142(4):1180, 2013.
- E. A. Maguire, E. R. Valentine, J. M. Wilding, and N. Kapur. Routes to remembering: the brains behind superior memory. *Nature neuroscience*, 6(1):90–95, 2003.
- J. R. Manning, S. M. Polyn, G. H. Baltuch, B. Litt, and M. J. Kahana. Oscillatory patterns in temporal lobe reveal context reinstatement during memory search. *Proceedings of the National Academy of Sciences*, 108(31):12893–12897, 2011.
- E. Maris and R. Oostenveld. Nonparametric statistical testing of eeg-and meg-data. *Journal of neuroscience methods*, 164(1):177–190, 2007.
- D. Marr. Simple memory: a theory for archicortex. *Philosophical Transac-*

- tions of the Royal Society of London. Series B, Biological Sciences*, pages 23–81, 1971.
- W. L. McFarland, H. Teitelbaum, and E. K. Hedges. Relationship between hippocampal theta activity and running speed in the rat. Technical report, ARMED FORCES RADIOBIOLOGY RESEARCH INST BETHESDA MD, 1974.
- J. L. McGaugh. Memory—a century of consolidation. *Science*, 287(5451): 248–251, 2000.
- M. B. Merkow, J. F. Burke, and M. J. Kahana. The human hippocampus contributes to both the recollection and familiarity components of recognition memory. *Proceedings of the National Academy of Sciences*, 112(46): 14378–14383, 2015.
- L. Mickes, T. M. Seale-Carlisle, and J. T. Wixted. Rethinking familiarity: Remember/know judgments in free recall. *Journal of memory and language*, 68(4):333–349, 2013.
- G. A. Miller. The magical number seven, plus or minus two: some limits on our capacity for processing information. *Psychological review*, 63(2): 81, 1956.
- J. F. Miller, E. M. Lazarus, S. M. Polyn, and M. J. Kahana. Spatial clustering during memory search. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 39(3):773, 2013a.
- J. F. Miller, M. Neufang, A. Solway, A. Brandt, M. Trippel, I. Mader, S. Hefft, M. Merkow, S. M. Polyn, J. Jacobs, et al. Neural activity in human hippocampal formation reveals the spatial context of retrieved memories. *Science*, 342(6162):1111–1114, 2013b.
- R. Miller. *Cortico-hippocampal interplay and the representation of contexts in the brain*, volume 17. Springer Science & Business Media, 2013.
- K. Mizuseki, A. Sirota, E. Pastalkova, and G. Buzsáki. Theta oscillations provide temporal windows for local circuit computation in the entorhinal-hippocampal loop. *Neuron*, 64(2):267–280, 2009.
- M. Montessori. *The montessori method*. Transaction publishers, 2013.

- S. M. Montgomery and G. Buzsáki. Gamma oscillations dynamically couple hippocampal ca3 and ca1 regions during memory task performance. *Proceedings of the National Academy of Sciences*, 104(36):14495–14500, 2007.
- F. J. Moreno-Martínez and P. R. Montoro. An ecological alternative to snodgrass & vanderwart: 360 high quality colour images with norms for seven psycholinguistic variables. *PloS one*, 7(5):e37527, 2012.
- R. Morris. Theories of hippocampal function. 2007.
- M. Moscovitch, R. S. Rosenbaum, A. Gilboa, D. R. Addis, R. Westmacott, C. Grady, M. P. McAndrews, B. Levine, S. Black, G. Winocur, et al. Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. *Journal of anatomy*, 207(1):35–66, 2005.
- E. I. Moser, E. Kropff, and M.-B. Moser. Place cells, grid cells, and the brain’s spatial representation system. *Annu. Rev. Neurosci.*, 31:69–89, 2008.
- M.-B. Moser, D. C. Rowland, and E. I. Moser. Place cells, grid cells, and memory. *Cold Spring Harbor perspectives in biology*, 7(2):a021808, 2015.
- R. Mukamel and I. Fried. Human intracranial recordings and cognitive neuroscience. *Annual review of psychology*, 63:511–537, 2012.
- S. L. Mullally, H. Intraub, and E. A. Maguire. Attenuated boundary extension produces a paradoxical memory advantage in amnesic patients. *Current Biology*, 22(4):261–268, 2012.
- G. E. Müller and A. Pilzecker. *Experimentelle beiträge zur lehre vom gedächtniss*, volume 1. JA Barth, 1900.
- R. U. Muller and J. L. Kubie. The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. *Journal of Neuroscience*, 7(7):1951–1968, 1987.
- R. U. Muller, J. L. Kubie, E. Bostock, J. Taube, and G. Quirk. Spatial firing correlates of neurons in the hippocampal formation of freely moving rats. 1991.

- K. Murnane and M. P. Phelps. When does a different environmental context make a difference in recognition? a global activation model. *Memory & Cognition*, 22(5):584–590, 1994.
- L. Nadel. The hippocampus and context revisited. *Hippocampal Place Fields: Relevance to Learning and Memory: Relevance to Learning and Memory*, page 1, 2008.
- L. Nadel and O. Hardt. Update on memory systems and processes. *Neuropsychopharmacology*, 36(1):251–273, 2011.
- L. Nadel and M. Moscovitch. Memory consolidation, retrograde amnesia and the hippocampal complex. *Current opinion in neurobiology*, 7(2):217–227, 1997.
- Z. Noh, M. S. Sunar, and Z. Pan. A review on augmented reality for virtual heritage system. In *Learning by Playing. Game-based Education System Design and Development*, pages 50–61. Springer, 2009.
- M. S. Nokia, M. Penttonen, T. Korhonen, and J. Wikgren. Hippocampal theta (3–8hz) activity during classical eyeblink conditioning in rabbits. *Neurobiology of learning and memory*, 90(1):62–70, 2008.
- N. Ohkawa, Y. Saitoh, A. Suzuki, S. Tsujimura, E. Murayama, S. Kosugi, H. Nishizono, M. Matsuo, Y. Takahashi, M. Nagase, et al. Artificial association of pre-stored information to generate a qualitatively new memory. *Cell reports*, 11(2):261–269, 2015.
- J. O’Keefe. Place units in the hippocampus of the freely moving rat. *Experimental neurology*, 51(1):78–109, 1976.
- J. O’Keefe and J. Dostrovsky. The hippocampus as a spatial map. preliminary evidence from unit activity in the freely-moving rat. *Brain research*, 34(1):171–175, 1971.
- J. O’Keefe and L. Nadel. *The Hippocampus as a Cognitive Map*. Oxford University Press, 1978.
- J. O’Keefe and M. L. Recce. Phase relationship between hippocampal place units and the eeg theta rhythm. *Hippocampus*, 3(3):317–330, 1993.
- D. Pacheco, S. Wierenga, P. Omedas, S. Wilbricht, H. Knoch, and P. F.

- Verschure. Spatializing experience: a framework for the geolocalization, visualization and exploration of historical data using vr/ar technologies. In *Proceedings of the 2014 Virtual Reality International Conference*, page 1. ACM, 2014.
- D. Pacheco, S. Wierenga, P. Omedas, L. S. Oliva, S. Wilbricht, S. Billib, H. Knoch, and P. F. Verschure. A location-based augmented reality system for the spatial interaction with historical datasets. In *Digital Heritage, 2015*, volume 1, pages 393–396. IEEE, 2015.
- D. Pacheco, M. Sánchez-Fibla, A. Duff, and P. F. Verschure. A spatial-context effect in recognition memory. *Frontiers in Behavioral Neuroscience*, 11:143, 2017.
- G. Papagiannakis, S. Schertenleib, B. O’Kennedy, M. Arevalo-Poizat, N. Magnenat-Thalmann, A. Stoddart, and D. Thalmann. Mixing virtual and real scenes in the site of ancient pompeii. *Computer Animation and Virtual Worlds*, 16(1):11–24, 2005.
- S. Papert. *Mindstorms: Children, computers, and powerful ideas*. Basic Books, Inc., 1980.
- S. Park, E. E. Kramer, V. Mercaldo, A. J. Rashid, N. Insel, P. W. Frankland, and S. A. Josselyn. Neuronal allocation to a hippocampal engram. *Neuropsychopharmacology*, 41(13):2987–2993, 2016.
- I. Pavlov. Conditioned reflexes: An investigation into the physiological activity of the cortex. *Trans. G. Anrep*. New York: Dover, 1927.
- M. A. Peterson. Object recognition processes can and do operate before figure-ground organization. *Current Directions in Psychological Science*, 3(4):105–111, 1994.
- M. A. Peterson and B. S. Gibson. Must figure-ground organization precede object recognition? an assumption in peril. *Psychological Science*, 5(5): 253–259, 1994.
- B. E. Pfeiffer and D. J. Foster. Hippocampal place cell sequences depict future paths to remembered goals. *Nature*, 497(7447):74, 2013.

- J. Piaget. The origins of intelligence in children. *Journal of Consulting Psychology*, 17(6):467, 1953.
- S. Pieper, M. Halle, and R. Kikinis. 3d slicer. In *Biomedical Imaging: Nano to Macro, 2004. IEEE International Symposium on*, pages 632–635. IEEE, 2004.
- P. L. Pirolli. *Information foraging theory: Adaptive interaction with information*. Oxford University Press, 2007.
- S. M. Polyn, V. S. Natu, J. D. Cohen, and K. A. Norman. Category-specific cortical activity precedes retrieval during memory search. *Science*, 310(5756):1963–1966, 2005.
- S. M. Polyn, K. A. Norman, and M. J. Kahana. A context maintenance and retrieval model of organizational processes in free recall. *Psychological review*, 116(1):129, 2009.
- M.-m. Poo, M. Pignatelli, T. J. Ryan, S. Tonegawa, T. Bonhoeffer, K. C. Martin, A. Rudenko, L.-H. Tsai, R. W. Tsien, G. Fishell, et al. What is memory? the present state of the engram. *BMC biology*, 14(1):40, 2016.
- A. Principe, M. Calabria, A. Tauste, J. Cruzat, G. Conesa, A. Costa, and R. Rocamora. Whole network, temporal and parietal lobe contributions to the earliest phases of language production. *Cortex*, 2017.
- R. Q. Quiroga. Concept cells: the building blocks of declarative memory functions. *Nature reviews. Neuroscience*, 13(8):587, 2012.
- R. Q. Quiroga, L. Reddy, G. Kreiman, C. Koch, and I. Fried. Invariant visual representation by single neurons in the human brain. *Nature*, 435(7045):1102–1107, 2005.
- S. Ramirez, X. Liu, P.-A. Lin, J. Suh, M. Pignatelli, R. L. Redondo, T. J. Ryan, and S. Tonegawa. Creating a false memory in the hippocampus. *Science*, 341(6144):387–391, 2013.
- C. Ranganath and M. Ritchey. Two cortical systems for memory-guided behaviour. *Nature reviews. Neuroscience*, 13(10):713, 2012.
- A. J. Rashid, C. Yan, V. Mercaldo, H.-L. L. Hsiang, S. Park, C. J. Cole, A. De Cristofaro, J. Yu, C. Ramakrishnan, S. Y. Lee, et al. Competition

- between engrams influences fear memory formation and recall. *Science*, 353(6297):383–387, 2016.
- C. Rennó-Costa, J. E. Lisman, and P. F. Verschure. The mechanism of rate remapping in the dentate gyrus. *Neuron*, 68(6):1051–1058, 2010.
- C. Rennó-Costa, J. E. Lisman, and P. F. Verschure. A signature of attractor dynamics in the ca3 region of the hippocampus. 2014.
- E. Reponen, T. Koponen, J. Keränen, and K. Väänänen-Vainio-Mattila. The whole world under your feet: field trial of embodied browsing of geotagged content. In *Proceedings of the Sixth International Conference on Tangible, Embedded and Embodied Interaction*, pages 291–298. ACM, 2012.
- H. G. Rey, I. Fried, and R. Q. Quiroga. Timing of single-neuron and local field potential responses in the human medial temporal lobe. *Current Biology*, 24(3):299–304, 2014.
- B. A. Richards and P. W. Frankland. The persistence and transience of memory. *Neuron*, 94(6):1071–1084, 2017.
- M. Ritchey, E. A. Wing, K. S. LaBar, and R. Cabeza. Neural similarity between encoding and retrieval is related to memory via hippocampal interactions. *Cerebral Cortex*, 23(12):2818–2828, 2012.
- E. T. Rolls. The mechanisms for pattern completion and pattern separation in the hippocampus. *Frontiers in systems neuroscience*, 7, 2013.
- B. Rossion and G. Pourtois. Revisiting snodgrass and vanderwart’s object pictorial set: The role of surface detail in basic-level object recognition. *Perception*, 33(2):217–236, 2004.
- D. C. Rowland, Y. Roudi, M.-B. Moser, and E. I. Moser. Ten years of grid cells. *Annual review of neuroscience*, 39:19–40, 2016.
- R. A. Ruddle, E. Volkova, and H. H. Bühlhoff. Walking improves your cognitive map in environments that are large-scale and large in extent. *ACM Transactions on Computer-Human Interaction (TOCHI)*, 18(2):10, 2011a.
- R. A. Ruddle, E. Volkova, B. Mohler, and H. H. Bühlhoff. The effect of land-

- mark and body-based sensory information on route knowledge. *Memory & Cognition*, 39(4):686–699, 2011b.
- M. D. Rugg and K. Allan. Event-related potential studies of memory. *The Oxford handbook of memory*, pages 521–537, 2000.
- M. D. Rugg and T. Curran. Event-related potentials and recognition memory. *Trends in cognitive sciences*, 11(6):251–257, 2007.
- U. Rutishauser, A. N. Mamelak, and E. M. Schuman. Single-trial learning of novel stimuli by individual neurons of the human hippocampus-amygdala complex. *Neuron*, 49(6):805–813, 2006.
- U. Rutishauser, I. B. Ross, A. N. Mamelak, and E. M. Schuman. Human memory strength is predicted by theta-frequency phase-locking of single neurons. *Nature*, 464(7290):903–907, 2010.
- U. Rutishauser, S. Ye, M. Koroma, O. Tudusciuc, I. B. Ross, J. M. Chung, and A. N. Mamelak. Representation of retrieval confidence by single neurons in the human medial temporal lobe. *Nature neuroscience*, 18(7):1041–1050, 2015.
- J. D. Ryan, R. R. Althoff, S. Whitlow, and N. J. Cohen. Amnesia is a deficit in relational memory. *Psychological Science*, 11(6):454–461, 2000.
- T. Sadeh, J. D. Ozubko, G. Winocur, and M. Moscovitch. How we forget may depend on how we remember. *Trends in cognitive sciences*, 18(1):26–36, 2014.
- D. M. Salz, Z. Tiganj, S. Khasnabish, A. Kohley, D. Sheehan, M. W. Howard, and H. Eichenbaum. Time cells in hippocampal area ca3. *Journal of Neuroscience*, 36(28):7476–7484, 2016.
- D. L. Schacter. Priming and multiple memory systems: Perceptual mechanisms of implicit memory. *Journal of Cognitive Neuroscience*, 4(3):244–256, 1992.
- D. L. Schacter and D. R. Addis. On the nature of medial temporal lobe contributions to the constructive simulation of future events. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, 364(1521):1245–1253, 2009.

- D. L. Schacter, J. E. Eich, and E. Tulving. Richard semon's theory of memory. *Journal of Verbal Learning and Verbal Behavior*, 17(6):721–743, 1978.
- D. Schiller, H. Eichenbaum, E. A. Buffalo, L. Davachi, D. J. Foster, S. Leutgeb, and C. Ranganath. Memory and space: towards an understanding of the cognitive map. *Journal of Neuroscience*, 35(41):13904–13911, 2015.
- K. Schrier. Using augmented reality games to teach 21st century skills. In *ACM SIGGRAPH 2006 Educators program*, page 15. ACM, 2006.
- W. B. Scoville and B. Milner. Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery & Psychiatry*, 20(1):11–21, 1957.
- M. A. Seager, L. D. Johnson, E. S. Chabot, Y. Asaka, and S. D. Berry. Oscillatory brain states and learning: Impact of hippocampal theta-contingent training. *Proceedings of the National Academy of Sciences*, 99(3):1616–1620, 2002.
- P. B. Sederberg, A. Schulze-Bonhage, J. R. Madsen, E. B. Bromfield, D. C. McCarthy, A. Brandt, M. S. Tully, and M. J. Kahana. Hippocampal and neocortical gamma oscillations predict memory formation in humans. *Cerebral Cortex*, 17(5):1190–1196, 2006.
- P. B. Sederberg, A. Schulze-Bonhage, J. R. Madsen, E. B. Bromfield, B. Litt, A. Brandt, and M. J. Kahana. Gamma oscillations distinguish true from false memories. *Psychological Science*, 18(11):927–932, 2007.
- P. B. Sederberg, J. F. Miller, M. W. Howard, and M. J. Kahana. The temporal contiguity effect predicts episodic memory performance. *Memory & Cognition*, 38(6):689–699, 2010.
- R. W. Semon. *The mneme*. G. Allen & Unwin Limited, 1921.
- A. G. Siapas, E. V. Lubenov, and M. A. Wilson. Prefrontal phase locking to hippocampal theta oscillations. *Neuron*, 46(1):141–151, 2005.
- D. Silva, T. Feng, and D. J. Foster. Trajectory events across hippocampal place cells require previous experience. *Nature neuroscience*, 18(12):1772, 2015.

- A. C. Singer, M. F. Carr, M. P. Karlsson, and L. M. Frank. Hippocampal swr activity predicts correct decisions during the initial learning of an alternation task. *Neuron*, 77(6):1163–1173, 2013.
- C. N. Smith, J. T. Wixted, and L. R. Squire. The hippocampus supports both recollection and familiarity when memories are strong. *The Journal of Neuroscience*, 31(44):15693–15702, 2011.
- S. M. Smith. Environmental context and recognition memory reconsidered. *Bulletin of the Psychonomic Society*, 23(3):173–176, 1985.
- S. M. Smith and E. Vela. Environmental context-dependent memory: A review and meta-analysis. *Psychonomic bulletin & review*, 8(2):203–220, 2001.
- S. M. Smith, A. Glenberg, and R. A. Bjork. Environmental context and human memory. *Memory & Cognition*, 6(4):342–353, 1978.
- T. Solstad, C. N. Boccara, E. Kropff, M.-B. Moser, and E. I. Moser. Representation of geometric borders in the entorhinal cortex. *Science*, 322(5909):1865–1868, 2008.
- E. Y. Song, Y. B. Kim, Y. H. Kim, and M. W. Jung. Role of active movement in place-specific firing of hippocampal neurons. *Hippocampus*, 15(1):8–17, 2005.
- L. R. Squire. The legacy of patient hm for neuroscience. *Neuron*, 61(1):6–9, 2009.
- L. R. Squire and A. J. Dede. Conscious and unconscious memory systems. *Cold Spring Harbor perspectives in biology*, 7(3):a021667, 2015.
- L. R. Squire and S. Zola-Morgan. The medial temporal lobe memory system. *Science*, 253(5026):1380–1386, 1991.
- L. R. Squire, J. T. Wixted, and R. E. Clark. Recognition memory and the medial temporal lobe: a new perspective. *Nature reviews. Neuroscience*, 8(11):872, 2007.
- B. P. Staresina, R. N. Henson, N. Kriegeskorte, and A. Alink. Episodic reinstatement in the medial temporal lobe. *Journal of Neuroscience*, 32(50):18150–18156, 2012.

- B. P. Staresina, T. O. Bergmann, M. Bonnefond, R. Van Der Meij, O. Jensen, L. Deuker, C. E. Elger, N. Axmacher, and J. Fell. Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. *Nature neuroscience*, 18(11):1679, 2015.
- B. P. Staresina, S. Michelmann, M. Bonnefond, O. Jensen, N. Axmacher, and J. Fell. Hippocampal pattern completion is linked to gamma power increases and alpha power decreases during recollection. *Elife*, 5:e17397, 2016.
- T. Staudigl and S. Hanslmayr. Theta oscillations at encoding mediate the context-dependent nature of human episodic memory. *Current Biology*, 23(12):1101–1106, 2013.
- S. Steinvorth, B. Levine, and S. Corkin. Medial temporal lobe structures are needed to re-experience remote autobiographical memories: evidence from hm and wr. *Neuropsychologia*, 43(4):479–496, 2005.
- S. Steinvorth, C. Wang, I. Ulbert, D. Schomer, and E. Halgren. Human entorhinal gamma and theta oscillations selective for remote autobiographical memory. *Hippocampus*, 20(1):166–173, 2010.
- J. M. Stephen, D. M. Ranken, C. J. Aine, M. P. Weisend, and J. J. Shih. Differentiability of simulated meg hippocampal, medial temporal and neocortical temporal epileptic spike activity. *Journal of clinical neurophysiology*, 22(6):388–401, 2005.
- K. Sylva, A. Jolly, and J. S. Bruner. *Play, its role in development and evolution*. Basic Books, 1976.
- M. Takeuchi, H. Furuta, T. Sumiyoshi, M. Suzuki, Y. Ochiai, M. Hosokawa, M. Matsui, and M. Kurachi. Does sleep improve memory organization? *Frontiers in behavioral neuroscience*, 8:65, 2014.
- B.-K. Tan and H. Rahaman. Virtual heritage: Reality and criticism. In *CAAD Futures*, pages 143–156, 2009.
- M. J. Tarr and W. H. Warren. Virtual reality in behavioral neuroscience and beyond. *Nature neuroscience*, 5(11s):1089, 2002.
- J. S. Taube, R. U. Muller, and J. B. Ranck. Head-direction cells recorded

- from the postsubiculum in freely moving rats. i. description and quantitative analysis. *Journal of Neuroscience*, 10(2):420–435, 1990.
- J. S. Taube, S. Valerio, and R. M. Yoder. Is navigation in virtual reality with fmri really navigation? *Journal of cognitive neuroscience*, 25(7):1008–1019, 2013.
- R. M. Tavares, A. Mendelsohn, Y. Grossman, C. H. Williams, M. Shapiro, Y. Trope, and D. Schiller. A map for social navigation in the human brain. *Neuron*, 87(1):231–243, 2015.
- K. K. Tayler, K. Z. Tanaka, L. G. Reijmers, and B. J. Wiltgen. Reactivation of neural ensembles during the retrieval of recent and remote memory. *Current Biology*, 23(2):99–106, 2013.
- A. Terrazas, M. Krause, P. Lipa, K. M. Gothard, C. A. Barnes, and B. L. McNaughton. Self-motion and the hippocampal spatial metric. *Journal of Neuroscience*, 25(35):8085–8096, 2005.
- C. Tesche and J. Karhu. Theta oscillations index human hippocampal activation during a working memory task. *Proceedings of the National Academy of Sciences*, 97(2):919–924, 2000.
- H. F. Thomas Kersten, Maren Lindstaedt. 2004.
- E. C. Tolman et al. Cognitive maps in rats and men, 1948.
- S. Tonegawa, X. Liu, S. Ramirez, and R. Redondo. Memory engram cells have come of age. *Neuron*, 87(5):918–931, 2015.
- D. Tse, R. F. Langston, M. Kakeyama, I. Bethus, P. A. Spooner, E. R. Wood, M. P. Witter, and R. G. Morris. Schemas and memory consolidation. *Science*, 316(5821):76–82, 2007.
- E. Tulving. Episodic and semantic memory¹. *Organization of memory*, pages 381–402, 1972.
- E. Tulving. Memory and consciousness. *Canadian Psychology/Psychologie canadienne*, 26(1):1, 1985.
- E. Tulving. Episodic memory: From mind to brain. *Annual review of psychology*, 53(1):1–25, 2002.

- E. Tulving and D. M. Thomson. Encoding specificity and retrieval processes in episodic memory. *Psychological review*, 80(5):352, 1973.
- E. Tulving, D. L. Schacter, et al. Priming and human memory systems. *Science*, 247(4940):301–306, 1990.
- I. J. van der Ham, A. M. Faber, M. Venselaar, M. J. van Kreveld, and M. Löffler. Ecological validity of virtual environments to assess human navigation ability. *Frontiers in psychology*, 6, 2015.
- M. A. van Gerven, E. Maris, M. Sperling, A. Sharan, B. Litt, C. Anderson, G. Baltuch, and J. Jacobs. Decoding the memorization of individual stimuli with direct human brain recordings. *Neuroimage*, 70:223–232, 2013.
- C. H. Vanderwolf. Hippocampal electrical activity and voluntary movement in the rat. *Electroencephalography and clinical neurophysiology*, 26(4):407–418, 1969.
- I. V. Viskontas, B. J. Knowlton, P. N. Steinmetz, and I. Fried. Differences in mnemonic processing by neurons in the human hippocampus and parahippocampal regions. *Journal of cognitive neuroscience*, 18(10):1654–1662, 2006.
- J. L. Voss, B. D. Gonsalves, K. D. Federmeier, D. Tranel, and N. J. Cohen. Hippocampal brain-network coordination during volitional exploratory behavior enhances learning. *Nature neuroscience*, 14(1):115–120, 2011a.
- J. L. Voss, D. E. Warren, B. D. Gonsalves, K. D. Federmeier, D. Tranel, and N. J. Cohen. Spontaneous revisitation during visual exploration as a link among strategic behavior, learning, and the hippocampus. *Proceedings of the National Academy of Sciences*, 108(31):E402–E409, 2011b.
- A. D. Wagner, W. Koutstaal, and D. L. Schacter. When encoding yields remembering: insights from event-related neuroimaging. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, 354(1387):1307–1324, 1999.
- A. J. Watrous, I. Fried, and A. D. Ekstrom. Behavioral correlates of human

- hippocampal delta and theta oscillations during navigation. *Journal of Neurophysiology*, 105(4):1747–1755, 2011.
- A. J. Watrous, D. J. Lee, A. Izadi, G. G. Gurkoff, K. Shahlaie, and A. D. Ekstrom. A comparative study of human and rat hippocampal low-frequency oscillations during spatial navigation. *Hippocampus*, 23(8):656–661, 2013a.
- A. J. Watrous, N. Tandon, C. R. Conner, T. Pieters, and A. D. Ekstrom. Frequency-specific network connectivity increases underlie accurate spatiotemporal memory retrieval. *Nature neuroscience*, 16(3):349–356, 2013b.
- A. J. Watrous, J. Fell, A. D. Ekstrom, and N. Axmacher. More than spikes: common oscillatory mechanisms for content specific neural representations during perception and memory. *Current opinion in neurobiology*, 31:33–39, 2015.
- R. W. White and R. A. Roth. Exploratory search: Beyond the query-response paradigm. *Synthesis Lectures on Information Concepts, Retrieval, and Services*, 1(1):1–98, 2009.
- M. A. Wilson, B. L. McNaughton, et al. Reactivation of hippocampal ensemble memories during sleep. *Science*, 265(5172):676–679, 1994.
- P. N. Wilson, N. Foreman, R. Gillett, and D. Stanton. Active versus passive processing of spatial information in a computer-simulated environment. *Ecological Psychology*, 9(3):207–222, 1997.
- J. T. Wixted. Dual-process theory and signal-detection theory of recognition memory. *Psychological review*, 114(1):152, 2007.
- J. T. Wixted. Remember/know judgments in cognitive neuroscience: An illustration of the underrepresented point of view. *Learning & Memory*, 16(7):406–412, 2009.
- R. Wojciechowski, K. Walczak, M. White, and W. Cellary. Building virtual and augmented reality museum exhibitions. In *Proceedings of the ninth international conference on 3D Web technology*, pages 135–144. ACM, 2004.

- E. R. Wood, P. A. Dudchenko, R. J. Robitsek, and H. Eichenbaum. Hippocampal neurons encode information about different types of memory episodes occurring in the same location. *Neuron*, 27(3):623–633, 2000.
- C.-T. Wu, D. Haggerty, C. Kemere, and D. Ji. Hippocampal awake replay in fear memory retrieval. *Nature neuroscience*, 20(4):571, 2017.
- J.-Z. Xiang and M. Brown. Differential neuronal encoding of novelty, familiarity and recency in regions of the anterior temporal lobe. *Neuropharmacology*, 37(4):657–676, 1998.
- G. Xue, Q. Dong, C. Chen, Z. Lu, J. A. Mumford, and R. A. Poldrack. Greater neural pattern similarity across repetitions is associated with better memory. *Science*, 330(6000):97–101, 2010.
- R. B. Yaffe, M. S. Kerr, S. Damera, S. V. Sarma, S. K. Inati, and K. A. Zaghloul. Reinstatement of distributed cortical oscillations occurs with precise spatiotemporal dynamics during successful memory retrieval. *Proceedings of the National Academy of Sciences*, 111(52):18727–18732, 2014.
- R. B. Yaffe, A. Shaikhouni, J. Arai, S. K. Inati, and K. A. Zaghloul. Cued memory retrieval exhibits reinstatement of high gamma power on a faster timescale in the left temporal lobe and prefrontal cortex. *Journal of Neuroscience*, 37(17):4472–4480, 2017.
- F. Yates. The art of. *Memory. Harmondsworth: Penguin*, 1969.
- A. P. Yonelinas. Receiver-operating characteristics in recognition memory: evidence for a dual-process model. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 20(6):1341, 1994.
- J. M. Zacks, N. K. Speer, K. M. Swallow, T. S. Braver, and J. R. Reynolds. Event perception: a mind-brain perspective. *Psychological bulletin*, 133(2):273, 2007.
- H. Zhang, J. Fell, B. P. Staresina, B. Weber, C. E. Elger, and N. Axmacher. Gamma power reductions accompany stimulus-specific representations of dynamic events. *Current Biology*, 25(5):635–640, 2015.
- H. Zhang, L. Deuker, and N. Axmacher. Replay in humans—first evidence

and open questions. In *Cognitive Neuroscience of Memory Consolidation*, pages 251–263. Springer, 2017.