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**Mechanisms underlying memory
enhancement in humans**

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María del Mar Yebra Granados

MEng in Telecom Engineering

MEng in Bioengineering and Telemedicine

Advisor
Bryan Strange
PhD in Neuroscience

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A mi familia.

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Resumen

La memoria ha sido objeto de investigación desde 1800. A día de hoy sabemos que existen diversos factores que modulan la memoria como emociones, eventos inesperados y relaciones semánticas; pero aún se desconocen los mecanismos neurales subyacentes en humanos. En esta tesis se exploran las bases neurales de dos factores que influyen en la memoria: acción y novedad. El movimiento voluntario no ha sido tradicionalmente considerado como un factor que aumenta la memoria. Sin embargo, los primeros indicios de una posible relación entre memoria y movimiento voluntario provienen de estudios a finales de los años 60 en los que se observó cómo lesiones en la estructura fundamental de memoria en el cerebro, el hipocampo, provocaban hiperactividad en roedores. Más tarde, otros estudios han confirmado esta relación entre ejecución de movimientos voluntarios y actividad hipocampal en humanos, pero desde entonces hasta ahora poco se conoce a cerca de una posible relación entre los sistemas motor y de memoria más allá de que una representación activa de aquello que codificamos facilita su posterior recuerdo. En esta tesis se estudia la hipótesis de que movimientos voluntarios que se ejecutan a la vez que se codifica una información visual, completamente no relacionada con el movimiento realizado, influyen en su posterior recuerdo. Esta tesis da respuesta a esta pregunta, mediante una serie de experimentos conductuales, demostrando que el hecho de realizar un movimiento

voluntario aumenta la memoria de aquello que codificamos simultáneamente. Mediante técnicas de Resonancia Magnética Funcional y pupilometría se demuestra que este efecto es mediado por el sistema noradrenérgico. Además conectividad funcional entre el Locus Cerúleo –fuente fundamental de noradrenalina en el cerebro- y el giro parahipocampal –región que ejerce un rol importante en la codificación de memoria episódica- ha sido observado. Estos hallazgos implican que el hecho de realizar un movimiento voluntario podría provocar la liberación de noradrenalina en el Locus Cerúleo, que al llegar a áreas de memoria como el giro hipocampal, favorece el recuerdo de aquello que codificamos simultáneamente.

Otro factor que facilita la memoria es la novedad o lo inesperado, en definitiva, aquello que produce una discordancia entre aquello que esperamos (en base a predicciones basadas en el pasado) y aquello que en realidad ocurre. Lesiones en el hipocampo humano afectan la adquisición de nuevas memorias, lo que sugiere un posible rol de esta estructura en el procesamiento de estímulos novedosos. La respuesta del hipocampo a este tipo de estímulos ha sido estudiada en animales y en humanos mediante técnicas de neuroimagen funcional y neurofisiológicas pero poco se conoce aún acerca de los mecanismos neurales subyacentes que el hipocampo utiliza para responder ante la experiencia de algo novedoso. Por otro lado, el hipocampo se encuentra en el Lóbulo Temporal Medial y posee una estructura alargada. Se conocen diferencias anatómicas, funcionales, de conectividad e incluso a nivel de expresión genética de esta estructura a lo largo del eje longitudinal. Se ha demostrado en roedores un rol funcional de la frecuencia oscilatoria en la banda theta que decrece de partes dorsales a partes ventrales del hipocampo a la vez que se observa un aumento el tamaño

de la región de espacio en la que se activan las células de lugar. Una evaluación sistemática de las frecuencias gamma y theta a lo largo del eje longitudinal del hipocampo no ha sido descrita todavía en humanos. En esta tesis se ha estudiado la respuesta electrofisiológica mediante el análisis de registros intracraneales profundos - electroencefalografía intracraneal (iEEG)- en pacientes epilépticos resistentes a tratamiento farmacológico; para caracterizar la respuesta de diferentes porciones del hipocampo (cabeza, cuerpo y cola) ante estímulos novedosos. Una inversión de polaridad observada en los potenciales evocados entre la cabeza y la cola, nos llevan a sugerir la existencia de una posible fuente eléctrica para actividad evocada por novedad en la porción anterior del hipocampo. A nivel electrofisiológico diferentes porciones del hipocampo experimentan un incremento en su actividad en las bandas frecuenciales theta y gamma, reflejando posiblemente un incremento en la actividad local de cada porción longitudinal. Análisis de coherencia y seguimiento de fase revelan que diferentes porciones del hipocampo están sincronizadas de manera similar. A pesar de que un aumento de coherencia en la banda theta entre diferentes regiones del hipocampo durante el procesamiento de novedad ha sido observado, no se han encontrado dichas diferencias en los valores de sincronización de fase. Esta sincronización y consistencia de fase observada entre diferentes porciones del hipocampo nos llevaron a estudiar un patrón oscilatorio, observado previamente en roedores y en un número limitado de pacientes humanos, que muestra cómo oscilaciones en la banda theta viajan a lo largo del eje longitudinal del hipocampo (de partes posteriores a partes anteriores) denominado “ondas viajeras”. Esta tesis confirma la existencia ondas, no solo en la banda theta, sino también en la banda alpha; viajando a lo largo del eje longitudinal del hipocampo de partes posteriores a partes anteriores. Esto implica que diferentes

porciones del hipocampo experimentan diferentes fases al mismo tiempo, lo que podría representar un potencial mecanismo para la codificación de información. No se ha encontrado ninguna diferencia a lo largo del eje longitudinal en el acoplamiento entre bajas frecuencias y gamma. A pesar de las diferencias conocidas a lo largo del eje longitudinal junto con estudios anteriores que sugieren una disociación funcional entre porciones anteriores y posteriores del hipocampo en el procesamiento de la novedad, esta tesis sugiere propiedades comunes en la respuesta oscilatoria a lo largo del eje longitudinal.

Diferentes enfoques y modalidades han sido utilizados en esta tesis para estudiar diferentes factores que modulan la memoria en humanos. Esta tesis demuestra por primera vez que movimientos voluntarios aumentan la memoria de aquello que codificamos simultáneamente a través de un mecanismo noradrenérgico en humanos. Por otro lado una evaluación comprensiva de la respuesta neurofisiológica del hipocampo ante la novedad en humanos ha sido presentada, con énfasis en aspectos comunes entre diferentes frecuencias y diferencias en las propiedades de la respuesta a lo largo del eje longitudinal del hipocampo.

Abstract

Memory has been a focus of intensive research since the 1800s. Currently, we know of several factors that modulate episodic memory, such as emotions, reward, unexpected events and semantic relations. However the mechanisms underlying this modulation remain unknown in humans. This thesis explores the neural bases of two factors which influence memory –actions and unexpectedness. Movement is not typically considered a factor that modulates memory but in the 1960s a possible relationship between movement and memory was suggested by evidence that lesions of the hippocampus—a region with a key role in episodic memory- provoked hyperactivity in rodents. Later studies in humans have confirmed a relationship between voluntary movement and hippocampal activity, but little is currently known about the relationship between motor and memory systems. In this thesis the hypothesis that voluntary movements, completely unrelated with the memory content, influence episodic memory is tested in humans. Across a series of behavioral experiments, a voluntary movement-evoked episodic memory enhancement was found. Furthermore, fMRI and pupilometry analysis revealed that this memory enhancement is mediated by the noradrenergic system. In addition, functional connectivity was observed between the Locus Coeruleus –the main source of noradrenaline in the brain-, and the parahippocampal gyrus –a region known to represent an important role in episodic memory encoding. This implies that a

voluntary movement triggers the release of noradrenaline in the brain that targets memory areas to promote episodic memory encoding.

Another factor known to modulate episodic memory is novelty, which can be defined as any event that represents a mismatch between expectation and experience. Hippocampal damage impairs the acquisition of novel episodic memories, which may suggest a role in processing novel stimuli. Hippocampal responses to novelty stimuli has been studied in animals and humans with different functional neuroimaging and electrophysiological techniques, however differences in the novelty processing along the long axis of the hippocampus remain unknown. Anatomical, functional, connectivity and genetic differences have been shown along the long axis of the hippocampus. A functional role of theta oscillatory frequency has been ascribed along the longitudinal axis in rodents decreasing from dorsal to ventral portions in rodents concomitant with an increase in place field size. A systematic evaluation of gamma and theta frequencies along the longitudinal axis has not been done in humans. In this thesis electrophysiological correlates with novelty have been studied along the longitudinal axis of the human hippocampus in pharmaco-resistant epileptic patients using intracranial electroencephalography (iEEG) recordings. A polarity inversion of the event related potential between the head and the body observed, lead us to suggest a possible electrical novelty-evoked source within the anterior portion of the hippocampus. Different portions of the hippocampus (head, body and tail) show a within-region power increase in theta and gamma frequency bands, reflecting increased local activity in each longitudinal portion during novelty processing. Analysis of phase locking value and imaginary coherence revealed between-region theta coherence increase. However, phase

locking values were not affected by unexpectancy indicating that different portions of the hippocampus were similarly synchronized. This consistent phase relationship in theta between portions of the hippocampus led us to test for the presence of traveling waves along the hippocampal long-axis (as has been recently shown in rodents and in limited number of human patients). We confirmed theta (and alpha) traveling wave pattern along the long axis of the hippocampus from posterior to anterior segments. This implies that the hippocampus experiences different phases of theta and alpha frequencies at the same time, potentially representing a mechanism for coding information. No differences on the lower frequencies modulating the gamma envelope during novelty processing across the long-axis were observed. Despite known differences along the long axis of the hippocampus and previous studies showing a functional segregation in novelty processing between anterior and posterior hippocampal portions, results in this thesis suggest common oscillatory response properties across the long-axis.

Different approaches have been used in this thesis to study different factors that modulate episodic memory in humans: actions and novelty. The first demonstration of voluntary movement-evoked modulation of memory for stimuli unrelated to the action is described, as well as a mechanistic account for this effect mediated by noradrenergic system. Next, a comprehensive evaluation of the electrophysiological response to novelty in human hippocampus is presented, with focus on commonalities and differences in response properties along the different portions of the hippocampal long axis.

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Chapter 1

General introduction

1.1 Memory and the Brain

Functional specialisation in the brain has been acknowledged since the 19th century, following the observations of lesioned patients such as Phineas Gage (1848) and the observations of Broca (1861) and Wernicke (1874). These findings gave rise to the theory of modularity suggesting that there are functionally specialized regions in the brain that are domain-specific for different cognitive processes. In the late 1920s Lashley came up with “law of mass action” in an attempt to find specific localization of areas responsible for learning and memory functions (hypothesized as engrams). This law stated that the memory defect subsequent to brain damage was dependent upon the size of the cortical area lesioned, not on its specific location as he found memories were not localized but widely distributed across the cortex (Lashley, 1929).

However it was not until the 1950s that a specific memory function was localised to a specific neuroanatomical region. This was possible by means of the observation of the famous patient HM (Henry Molaison) who had a bilateral medial-temporal lobectomy to resect the anterior two thirds of his hippocampi, parahippocampal cortices, entorhinal cortices, piriform cortices, and amygdalae in an attempt to cure his severe epilepsy. Scoville and Milner (1957) reported an evident memory impairment immediately after the surgery. Although HM was unable to acquire any new memories that could be later recalled, old memories from his childhood seemed to be intact (Scoville & Milner, 1957) and his bilateral medial temporal lobectomy did not impair the acquisition of new motor skills (Milner, 1962). Furthermore, HM was able to register perceptual information normally, but this information ceased to be available to him after 30-40

seconds (Milner, 1972). However, later studies of patient HM showed that at the age of 72 relatively spared semantic memory, but severe impairment on measures of autobiographical memory, with no temporal gradient (Steinvorth, Levine, & Corkin, 2005). This finding stimulated discussion about the nature and significance of retrograde amnesia, although later MRI scans of patient HM revealed changes since his first MRI including cortical thinning, subcortical atrophy, large amounts of abnormal white matter, and subcortical infarcts (Salat, et al., 2006). The study of other patients, EP and GP with similar methods used by Steinvorth and colleagues argued that autobiographical recollection was impaired when memories were drawn from the recent past but fully intact when memories were drawn from the remote past (Kirwan, Bayley, Galván, & Squire, 2008). Together these findings suggest that remote memories in patient HM could have been intact in the early years after surgery but then have faded with time because they could not be strengthened through rehearsal and relearning (Squire, 2009).

In any case, these early findings provided evidence for dissociable memory systems in the brain. Patient HM and the study of other amnesic patients led to a classification of memory types depending on medial temporal lobe integrity. This classification addresses long-term memory, and not short-term memory, (e.g., digit-span), which is intact following medial temporal damage (Shallice & Warrington, 1970). Two main types of long term memory are commonly distinguished: declarative or explicit and non-declarative or implicit (Cohen & Squire, 1980).

Non-declarative memory is fully intact in patients with hippocampal damage (Squire, Knowlton, & Musen, 1993). It is acquired and used without providing conscious access to any prior episodes (Schacter & Tulving, 1994), and can affect thoughts and behaviours. It is related to skilled behaviour and habits (procedural memory), such as riding a bike, and provides the ability to respond correctly to stimuli as a result of conditioning or habit learning. It also includes changes in the ability to process objects as a result of recent encounters, a phenomenon known as priming (Warrington & Weiskrantz, 1968). Perceptual priming is thought to be mediated by higher visual cortical areas, such as inferior temporal regions (Schacter & Buckner, 1998). Non-declarative memory is slow in acquisition (priming is an exception) and reliable.

Declarative memory is dependent on the medial temporal lobes and affords the capacity for conscious, intentional recollection of factual information, previous experiences and concepts (Squire, 1992). Declarative memory is propositional, being either true or false. It is fast in acquisition, not always reliable (i.e. forgetting and retrieval failure can occur), and flexible in the sense that declarative memories are accessible to multiple response systems. Declarative memory can be further divided into two categories: episodic memory, which stores specific personal experiences, and semantic memory, which stores factual information that is independent of the specific episodes in which that information was acquired (Tulving, 1972).

Patient H.M.'s severe memory impairment led to intensive study of patients and animal models with hippocampal damage, with an ensuing characterization of hippocampal function in terms of declarative memory (Squire, 1992), encompassing both episodic

and semantic memory. There is a consensus on the hippocampus, which is a medial temporal lobe structure, being critically involved in episodic memory (Aggleton & Brown, 1999; Eichenbaum, 2001; Kinsbourne, & Wood, 1975; Lepage, Habib, & Tulving, 1998; O'Keefe & Nadel, 1978; Scoville, & Milner, 1957; Squire, 1992; Squire, Zola-Morgan, & Stuart, 1991; Strange, Fletcher, Henson, Friston, & Dolan, 1999a; Tulving, 1985; Vargha-Khadem et al., 1997). However, episodic memory was only one of several functions being ascribed to the hippocampus at the time.

1.1.1 Anatomy of the hippocampus

The human hippocampus is located in the medial temporal lobe, lying on the floor of the inferior horn of the lateral ventricle. The hippocampus proper is composed of the CA (cornu ammonis) subfields whereas the hippocampal formation includes the dentate gyrus (DG), CA subfields and subiculum. All hippocampal components are composed of simple three-layered allocortex, which differentiates them from surrounding six-layered medial temporal neocortex, the entorhinal, perirhinal and parahippocampal cortices (Witter, 1993).

The hippocampus forms an arc whose anterior extremity is enlarged and whose posterior extremity narrows like a comma. The hippocampus can be divided into three parts: (1) an anterior part, or head, (2) a middle part, or body, and (3) a posterior part, or tail. It has a total length of between 4 and 4.5 cm; the body is on average 1 cm wide, and the head is 1.5–2 cm wide (Duvernou, 2005).

Its long, curved form is present across all mammalian orders. It runs along a dorsal (septal)-to-ventral (temporal) axis in rodents, corresponding to a posterior-to-anterior axis in humans and non-human primates. There is currently no precise anatomical definition for a dorsal (or posterior) portion of the hippocampus relative to a ventral (or anterior) one, although in general, the former is positioned close to the retrosplenial cortex and the latter close to the amygdaloid complex. Figure 1 schematically depicts the hippocampus across species. Note that a 90-degree rotation is required for the rat hippocampus to have the same orientation as that of primates. In primates, the anterior extreme is curved rostromedially to form the uncus (Strange, Witter, Lein, & Moser, 2014).

Figure 1. Cross-species comparison of hippocampal anatomy. a) Schematic of the orientation of the hippocampal long axis in rats, macaque monkeys and humans. b) The full long axis of the hippocampus (red) highlighted in brains of rats, macaque monkeys and humans, with the entorhinal cortex (EC) shown in blue. c) Drawings of Nissl cross-sections of mouse, rhesus and human hippocampi. A, anterior; C, caudal; D, dorsal; DG, dentate gyrus; L, lateral; M, medial; P, posterior; R, rostral; V, ventral. Panel taken from (Strange, Witter, Lein, & Moser, 2014).

Hippocampal connectivity is particularly suited in a way that it receives information not only about the external world through sensory inputs but also interoceptive information, from subcortical and brainstem systems, regarding the internal state of the organism (see Amaral & Witter, 1989 for review). Traditionally, there has been a classic ‘dorsal–ventral dichotomy view’ of the hippocampus, which has dominated the field proposing that anterior parts mediate emotional response (Gray & McNaughton, 2003) and dorsal parts mediate cognitive functions, particularly spatial memory (Bannerman, Rawlins, & McHugh, 2004; Fanselow & Dong, 2010). This is based on observations that emphasized the segregation of inputs to the hippocampus from cingulate areas (Canteras & Swanson, 1992; van Groen & Wyss, 1990). However, differences in connectivity with cortical and subcortical structures along the dorsoventral axis of the hippocampus are gradual rather than absolute (Amaral & Witter, 1989), which suggests that functional differences along the long axis may exhibit a gradient-like organization (Kjelstrup et al., 2008).

1.1.2 Theories of Hippocampal Function

In addition to episodic memory, hippocampus has been shown to play an important role in spatial navigation, novelty detection and action or action inhibition. With respect to spatial navigation vs. episodic memory functions, recent work argues that both are intrinsically linked, such that episodic memory requires a spatial context. This suggests that spatial mapping and navigation can be seen as an application of relational memory organization of experiences in memory (Eichenbaum, 2017) .

1.1.2.1 Hippocampus as a cognitive map

Cells in the hippocampal formation are thought to provide a representation of the environment, places and objects in it, and requires long-term memory for the spatial relationships between places, routes between them, resources, goals and hazards they may contain. These cells can represent current or heading location and its cells are anchored to the external environment rather than to individual objects, actions or to the body. This so called “Cognitive Map” theory was first described in 1948 (Tolman, 1948)

There are many different types of cells within the hippocampus, in this section four different type of spatial cells are going to be introduced: place cells, head direction cells, grid cells, and boundary cells (Hartley, Lever, Burgess, & O’Keefe, 2013; Moser, Rowland, & Moser, 2015).

1.1.2.1.1 Place cells

Place cells were discovered in the hippocampus of the freely behaving rat by O’Keefe & Dostrovsky in 1971. Place cells characteristically fire at a low rate throughout most of the environment, but each cell shows increased firing when the animal is within a specific location of the environment (its ‘place field’) (O’Keefe & Dostrovsky, 1971). Interestingly, more recent research in 2008 shows the size of place fields in CA3 increasing almost linearly from dorsal to ventral hippocampus from 1 meter to 10 metres approximately (Kjelstrup et al., 2008). In rats in which different place cells were recorded simultaneously at a certain location (place field), only a small subset of place

cells will fire strongly and simultaneously. These spatially specific firing patterns enable a highly accurate reconstruction of the current location of the rat (Wilson & McNaughton, 1994; Zhang, Ginzburg, McNaughton, & Sejnowski, 1998). Furthermore, place cell firing rates in the open field typically do not depend on the animal's orientation -head direction (HD)- or direction of travel (Muller, Bostock, Taube, & Kubie, 1994), and place fields remain the same even when individual cues are removed from the environment (O'Keefe & Nadel, 1978). However, removal of the most relevant cues can elicit remapping -change in tuning of the place cell firing in a different place field- (Lever, Wills, Cacucci, Burgess, & O'Keefe, 2002).

In 1993, O'Keefe & Recce observed a phenomenon called phase precession, which encapsulates a spatio-temporal code in the hippocampus. Phase precession leads the spiking within a place field to occur at earlier phases of the theta local field potential (LFP) as the rat progresses across the field (O'Keefe & Recce, 1993).

1.1.2.1.2 Head direction and boundary cells

After the discovery of place cells, it was not until 1990 when another type of cell in the hippocampus was discovered: head direction (HD) cells, that show a firing pattern selective to the head orientation independent of the location of the rat (Taube, Muller, & Ranck, 1990). Initially, head direction cells were found in the postsubiculum. Later, these cells were also found in other brain areas, including the entorhinal cortex (Sargolini et al., 2006), in the anterior thalamic nuclei (Taube, 1995), retrosplenial cortex (Cho & Sharp, 2001), lateral mammillary nuclei (Stackman & Taube, 1998). This type of cell firing pattern is tuned to the head direction, they fire rapidly whenever

the animal is facing in the preferred head direction and only weakly otherwise. Similarly with place cells, the monitoring of a subset of HD cells leads to a highly accurate reconstruction of the head direction of the rat (Johnson, Seeland, & Redish, 2005; Zhang, 1996). Interestingly, the preferred tuning of head direction cells can be rotated by moving visual cues, which also affects the location of place fields of place cells. Together with studies showing that lesions to the HD system disrupts the ability of visual cues to control the orientation of a place field and makes place cells more directional, this suggests that place cells rely on directional information from the HD system (Calton et al., 2003).

In 2000 O'Keefe and colleagues established a computational model of boundary vector cells (BVC), that describe place cells with extended firing fields parallel to the edges of the environment. These cells also exhibit additional place fields where new barriers were inserted (Hartley, Burgess, Lever, Cacucci, & O'Keefe, 2000). Cells with such characteristics were later discovered in the subiculum (Barry, Lever, Hayman, Hartley & O'Keefe, Jeffery, 2006; Lever, Burton, Jeewajee, O'Keefe & Burgess, 2009), MEC (Kjelstrup et al., 2008; Savelli, Yoganarasimha, & Knierim, 2008), presubiculum and parasubiculum (Boccaro et al., 2010).

1.1.2.1.3 Grid cells

More recently, a new type of spatial cell called grid cells have been discovered in the dorsocaudal medial entorhinal cortex (MEC) (Hafting, Fyhn, Molden, Moser, & Moser, 2005). These cells have been also found in pre- and parasubiculum (Boccaro et al., 2010). While place cells fire in a specific location, grid cell firing maps the environment

via their regular, hexagonal firing pattern. These cells exhibit enhanced autocorrelation of their firing rates whenever the animal's position coincides with any vertex of a regular grid of equilateral triangles spanning the surface of the environment. Grid cells can be described by three main features: scale, orientation and spatial phase. The scale is defined by the distance between adjacent peaks in the firing rates (lengths of the sides of the triangles). Orientation is given by the angle between the grid axes and some reference direction. Spatial phase is defined by the vertex locations of the triangles describing the grids. Interestingly, grid fields from different grid cells recorded from the same site can have widely differing spatial phases, so that they may be offset with respect to one another, even when they share the same scale and orientation. The regularity of the arrangement of these grid firing in multiple fields has led to the understanding of grid cells as a universal and environmental-invariant metric for navigation. However recent research indicates that environmental boundaries influence grid cell firing (Barry, Hayman, Burgess, & Jeffery, 2007) and that grid orientation, scale, symmetry and homogeneity are strongly and permanently affected by environmental geometry. The authors found that grid-patterns orient to the walls of polarised enclosures such as squares but not circles. Furthermore, the hexagonal grid-patterns also exhibited a permanent decrease in hexagonality in highly polarised environments such as trapezoids, the pattern being more elliptical and less homogeneous (Krupic, Bauza, Burton, Barry, & O'Keefe, 2015). Similarly to place cells, the scale of grids cells increases along dorsal to ventral axis, with lower scale in dorsal MEC compared to ventral locations (Hafting, Fyhn, Bonnevie, Moser, & Moser, 2008; Hafting et al., 2005). Another important difference along the long axis of MEC is that ventral MEC specifically supports navigation in the light, whereas the dorsal MEC,

rich in grid cells, supports navigation in the dark (Poucet et al., 2013). These data suggest that grid cells are involved in path integration that is the use of self-motion signals to compute travelled distances and directions, which in turn contributes to the maintenance of estimates of current location. They also may have a functional role in driving place cell remapping –change in tuning of the place cell firing in a different place field- and the formation of distinctive hippocampal codes for different environments (reviewed in Hartley et al., 2013). However, recent work suggested that new, highly distinct configurations of place fields emerged immediately after inactivation of the medial septal area, a manipulation known to disrupt theta oscillations (decrease in ~80% the amplitude of theta rhythm) and grid cell firing. These new place fields persist after theta oscillations had recovered (Brandon, Koenig, Leutgeb, & Leutgeb, 2014).

These evidence shows that the hippocampus provides representation of the environment, places and objects in it, and requires long-term memory for the spatial relationships between them. Not only is a key structure in spatial cognition, but also represent a role in relational organization and flexibility of cognitive maps. This might serve as a mechanism to organize experiences in memory that can be the prelude to integrative theories about linking neural coding, learning and memory.

1.1.2.2 Hippocampus and novelty.

Efficient memory encoding would restrict the incoming information to relevant inputs, since not every sensory input can be committed to memory. It is reasonable that we encode information in an efficient manner updating what we already know about the

world with new information we perceive, comparing the current “*model of reality*” with what is new in our environment. From this perspective, novelty has preferential access to memory systems as a key modulator and plays an important role in how we code new memories. A potential mechanism could be updating old memories by means of mismatch between expectancy and experience calculations.

Given that novelty processing implies a comparison between predictions and stored memories, this computation is likely to happen in the hippocampus. Many models of how novelty is processed and stored in to memory have been suggested from the early 60s until today

1.1.2.3.1 Hippocampus and novelty: animal models

In 1963, Sokolov suggested a model in which novel stimuli are used to generate a mismatch signal between the model of the stimuli in an environment maintained in the neocortex and the new incoming information (Figure 2). This mismatch signal engages the reticular formation to generate an orientating response attributing mismatch detection to a neocortical-reticular formation interaction (Sokolov & Ternov, 1963). Later, in 1990, Sokolov suggested that the hippocampus is involved in this mismatch detection by generating a neural model of the standard stimulus. This is also based on the observation that novelty detectors in the hippocampus mimic specific features of the orientating response such as habituation (Sokolov, 1990).

In 1975, evidence for novelty processing in the hippocampus was provided by, extracellular intracranial recordings from single-units in rabbits during stimulation with

sensory stimuli from different modalities (Figure 2). Any perceptible change of a signal, or the conditions of its presentation, caused the initial response to be reinstated. This study also supported the conclusion that hippocampal CA1 neurons were found to be much more stimulus-specific than CA3 neurons. CA3 neurons, in turn, were sensitive to the novelty of a stimulus (its absence in “trace storage”), not to its specific physical properties. It was also suggested that CA3 neurons acts as a trigger or gate, which only in some definite state (novelty, mismatch) allows passage of sensory signals to CA1 neurons (Vinogradova, 1975b).

It was in 1978 when O’Keefe and Nadel started to study place cells in CA1 and identified hippocampus involvement in novelty detection. Some cells in the hippocampus fired maximally when a rat attended to a certain place either because the object is usually there (e.g. reward), has been removed or, alternatively, because a novel object has been placed (O’Keefe & Nadel, 1978). Rank (1973) also found mismatch units primarily in CA1 in the hippocampus firing maximally when the rat went to a reward site and failed to find reward. Together, the evidence by O’Keefe and Rank suggested that the mismatch sensitivity found by Vinogradova in CA3 to be localised in CA1 (Figure 2).

Subsequently, in 1982, Gray developed a theory about mismatch detection in the hippocampal formation (Figure 2). Based on Vinogradova’s finding that single-cell responses to simple sensory stimuli are less specific to the parameters of the stimulus in the dentate gyrus than in entorhinal cortex (EC), Gray’s theory suggests that entorhinal cortex sends less specific information by a more circuitous route, via the dentate gyrus

and CA subfields to the subicular cortex. Entorhinal cortex also apparently sends more specific information directly to the subiculum. Thus, Gray proposes the dentate cells to be '*decision-makers*' on whether the less specific sensory information from the entorhinal cortex is important enough. In case of a "mismatch", the enabling signal from CA1 is sent to the subiculum cells which he suggests to be now the central comparator, based on behavioural experiments. In summary, Gray's theory set the incoming sensory information that is directly transmitted from entorhinal cortex to the subiculum, to be the *current state of the world*. This current state is matched against predicted sensory input to generate the next prediction, but only if it receives an enabling signal from CA1 that determines whether the description is treated as important (Gray, 1982).

Figure 2. Schematic of the models suggested of novelty processing. The older model is depicted in black: Novelty signals are used to calculate a mismatch signal between the model of the stimuli maintained in the neocortex and the new incoming information to generate an orientating response engaging the reticular formation (Sokolov & Ternov, 1963). Revised model, depicted in blue, incorporates the hippocampal formation as the novelty detector (Sokolov, 1990). Depicted in light green CA3 as a novelty gate of sensory signals to CA1 as a mismatch detector suggested by (Vinogradova, 1975a). In dark green, later incorporation of CA1 as mismatch detector in the hippocampus by (O'Keefe & Nadel, 1978; Rank, 1973). Depicted in purple updated schematic of novelty processing by (Gray, 1982). Incoming sensory information about the current state of the world is conveyed through the EC to the subiculum directly via a less circuitous route but sending more specific sensory information. Via a more circuitous route, sensory information is conveyed from the EC to DG which sends information only if relevant to CA1. Finally, the novelty signal is sent to the subiculum where the mismatch signal is then calculated comparing input from CA1 and EC.

The role of the hippocampus in novelty detection is further supported by the finding that interfering with hippocampal function inhibits the orienting of rabbits to novel stimulus configurations (Honey, Watt, & Good, 1998; Vinogradova, 2001). In addition, stimulation of the hippocampal region increases exploratory behaviour in a manner similar to that produced by novelty itself (Flicker & Geyer, 1982; Yang & Mogenson,

1987). Other recent studies using single-unit recordings (Fyhn, Molden, Hollup, Moser, & Moser, 2002; Vinogradova, 2001) and c-Fos expression (Jenkins, Amin, Pearce, Brown, & Aggleton, 2004) all indicate that presentation of a novel stimulus produces a robust increase in hippocampal activity.

Subsequently, other theories emerged arguing that the novelty signals detected in CA1 can be computed earlier on in regions that in the tri-synaptic anatomical circuit precede CA1, such as dentate and CA3 cells. Together with evidence of CA1 cells receiving incoming sensory information directly from the entorhinal cortex (Vinogradova, 1975a), a new model reviewed in (Lisman & Grace, 2005) suggests that CA1 is computing novelty by comparing predictions from a CA3-Dentate loop (with the dentate cells addressing the importance of the signal coming from the cortical sensory input from layer 2 of the entorhinal cortex) with the model of reality, arriving from layer 3 of the entorhinal cortex that processes cortical input (Figure 3).

Figure 3. Refined model for novelty processing. Sensory input is conveyed from layer 2 of the EC to the DG which signals only important information to CA1 through CA3. Model of reality is conveyed through layer 3 of EC to CA1. CA1 compares the prediction from CA3 and the sensory input from layer 3 of the EC and sends a novelty signal to the subiculum. (Model reviewed in Lisman & Grace, 2005).

1.1.2.3.2 Hippocampus and novelty: Human data.

Novelty can also be defined as detecting mismatches between expectation and experience as an essential mechanism to anticipate upcoming events. This mechanism has been widely studied using oddball paradigms, where the oddball stimuli represent a violation of expectation due to their deviance from the prevailing context (Rugg, 1995). Thus, these oddball paradigms have been widely used to study responses to violations of context by salient stimuli exposure (Kiehl, Laurens, Duty, Forster, & Liddle, 2001; Opitz, Mecklinger, Friederici, & von Cramon, 1999). As novel stimuli, can elicit surprise, are unpredictable and violate our predictable set about the world (Ebmeier et al., 1995).

However, physiological mechanisms underlying novelty detection in relation to long-term memory have yet to be understood in humans. It is known that in oddball paradigms the unexpected condition elicits a scalp recorded parietocentral event-related potential (ERP) response with a peak latency between 300 and 600 ms, known as P300 (Johnson, 1988; Picton, 1992). Intracranial recordings during oddball tasks in epileptic patients evoke large ERPs in the hippocampus in the unexpected condition, with a similar peak latency (Barbeau, Chauvel, Moulin, Regis, & Liégeois-Chauvel, 2016; Brázdil, Rektor, Daniel, Dufek, & Jurák, 2001; Grunwald, Beck, Lehnertz, et al., 1999; Halgren et al., 1995; Ludowig, Bien, Elger, & Rosburg, 2010; McCarthy, Wood, Williamson, & Spencer, 1989; Roman, Brázdil, Jurák, & Rektor, 2005). This hippocampal component has been termed “MTL P300” in reference to the novelty P300. Also, lesion studies demonstrated that this potential depends on a network including the hippocampus, showing reduced ERP signals in the hippocampus and reduced novelty-initiated galvanic skin response in patients with posterior hippocampal lesions (Knight & Nakada, 1998; Knight, 1996).

Furthermore, a positive component (P600) has also been reported in the hippocampus during recognition of famous faces, familiar visual patterns or previously learned words (Barbeau et al., 2008; Grunwald et al., 2003; Trautner et al., 2004). Recent work using intracranial hippocampal recordings in humans observed similar time courses for ERPs evoked in oddball and memory tasks, but with opposite polarity between 400 and 600 ms. For the oddball tasks, a negative peak resembling the novelty P300 was found, a positive peak for memory tasks akin to the hippocampal P600 was observed ~80ms later. Strikingly, this pattern disappears in contacts outside the hippocampus suggesting

that the same region of the hippocampus is processing memory and oddball task differently. The results are interpreted on the basis of two competing hypothesis: (1) either the direct (monosynaptic) and indirect (trisynaptic) entorhinal-hippocampal CA1 pathways subserve novelty and memory, respectively or (2) two distinct neuronal populations (CA1 pyramidal cells and dentate gyrus granule cells or another sector of CA) subserve novelty responses during oddball and memory tasks, respectively. Either way, these results once more argue in favour of a model in which CA1 integrates activities of two distinct large-scale networks implementing externally oriented –e.g. oddball tasks, requiring attention to external stimuli- or internally oriented –e.g. memory tasks, requiring attention to internal representations-, brain states (Barbeau et al., 2016).

Studies using PET (Tulving, Markowitsch, Craik, Habib, & Houle, 1996) and fMRI (Strange, & Dolan, 2001; Yamaguchi, Hale, D'Esposito, & Knight, 2004) also indicate that presentation of a novel stimulus produces a robust increase in hippocampal activity.

1.1.2.3.4 Brain circuits for Novelty Detection

Novelty detection is not only occurring in the hippocampus. There is also evidence for some of the major neurotransmitter systems being associated with novelty processing, including dopamine (DA) and norepinephrine (NE).

1.1.2.3.4.1 Dopamine

Lisman and colleagues (2005) reviewed the role of hippocampus in novelty detection and they suggest a model which closes the functional loop conveying the information

from the subiculum through the accumbens and ventral pallidum to the Ventral Tegmental Area (VTA). Subsequently VTA releases dopamine back to the hippocampus (CA1) promoting Long Term Potentiation (LTP) - a form of synaptic plasticity thought to represent the basis for learning and memory- to regulate the entry of information in long term memory (Lisman & Grace, 2005) (Figure 4). The VTA is a midbrain structure which dopamine cell bodies project to cortex and hippocampus (mesolimbic system) (Düzel et al., 2009). This functional loop is based on the idea of the hippocampus responding very rapidly to novelty (~100ms) (Brankačk, Seidenbecher & Müller-Gärtner, 1996; Grunwald, Lehnertz, Heinze, Helmstaedter & Elger, 1998; Ruusuvirta, Korhonen, Penttonen, Arikoski, & Kivirikko, 1995), suggesting that the hippocampus is more likely to first trigger the novelty-dependent firing of the VTA and later being modulated by the afferent dopaminergic projections from the VTA.

There is evidence suggesting a pathway conveying novelty information from VTA to the hippocampus, demonstrating VTA activation and DA release in the nucleus accumbens, which is a VTA target (Legault & Wise, 2001). On the one hand, the accumbens seems to respond to novelty (Ihalainen, Riekkinen Jr, & Feenstra, 1999) and to subiculum stimulation (Wood & Rebec, 2004). On the other hand, the accumbens sends inhibitory GABAergic input to the ventral pallidum, and those GABAergic neurons send projections to dopaminergic neurons in the VTA (Chrobak & Napier, 1993; Mogenson, Brudzynski, Wu, Yang & Yim, 1993). Direct infusion of GABA A/B agonists inhibits the ventral pallidum, increasing the number of DA neurons that are active in the VTA (because of disinhibition), mimicking the effect of subicular stimulation (Floresco, West, Ash, Moore, & Grace, 2003).

Together, this suggests a new model in which the subiculum sends excitatory glutamatergic projections to the accumbens, which in turn inhibits the ventral pallidum, thus releasing the VTA DA neurons from a tonic inhibitory influence (Lisman & Grace, 2005). There is also evidence in monkeys describing dopaminergic cell firing in novel situations. Unexpected reward can increase DA cell firing compared with a situation when expected reward is omitted (Schultz & Dickinson, 2000). However, DA firing triggered by novel stimuli that do not involve reward has also been reported (Horvitz, Stewart, & Jacobs, 1997; Ljungberg, Apicella, & Schultz, 1992; Steinfels, Heym, Strecker, & Jacobs, 1983). Work in cats and monkeys also shows that these cells respond to novelty and habituate when the stimulus becomes familiar (Ljungberg et al., 1992; Steinfels et al., 1983).

The hippocampus receives dopaminergic input (Gasbarri, Sulli, & Packard, 1997) and the pathways responsible for this novelty dependent dopaminergic activity can be traced back to the hippocampus (Legault & Wise, 2001). Particularly, the hippocampus receives dopaminergic projections (Gasbarri, Verney, Innocenzi, Campana, & Pacitti, 1994; Gasbarri et al., 1997; Goldsmith & Joyce, 1994) from the VTA and substantia nigra (SN) (Scatton, Simon, Le Moal, & Bischoff, 1980).

Evidence supporting DA affects long-term potentiation (LTP) was given by in vitro experiments showing that LTP in CA1 is strongly dependent on DA (Bach et al., 1999; Frey, Huang, & Kandel, 1993; Frey, Matthies, Reymann, & Matthies, 1991; Frey, Schroeder, & Matthies, 1990). The ability of a DA antagonist to block late LTP has been demonstrated in vitro (Frey et al., 1990; Morris et al., 2003) and also in vivo

(Swanson-Park et al., 1999). Late LTP differs from early LTP on that the former requires gene transcription and protein synthesis in the postsynaptic cell (Lynch, 2004). Furthermore, it has been shown that LTP can be enhanced by activation of dopamine receptors (Li, Cullen, Anwyl, & Rowan, 2003; Otmakhova & Lisman, 1996; Swanson-Park et al., 1999).

There is also evidence showing that exposure of rats to a novel environment increases DA release in the hippocampus (Ihalainen et al., 1999) and also enhances the ability of a weak tetanus – a stimulation normally not producing LTP- to induce LTP in CA1 (Li et al., 2003). Moreover, injection of D1 antagonist, but not cholinergic and noradrenergic, blocks this enhancement. If the rat is in a familiar cage D1 agonist enhances LTP in a similar way to that produced by placing the rat in a new environment (Li et al., 2003).

Figure 4. Refined model of novelty processing adding hippocampal-VTA loop (suggested in Lisman & Grace, 2005). The novelty signal from the subiculum is conveyed through the accumbens and ventral pallidum to the VTA which releases dopamine back to the hippocampus (CA1) promoting Long Term Potentiation (LTP).

Given DA enhancement of LTP, it is reasonable to expect that dopamine release enhances learning. There is evidence from animal studies showing that it is the case (Bach et al., 1999; Bernabeu et al., 1997; Packard & White, 1991). Indeed, systemic dopamine agonists strongly enhanced spatial memory in aged rats while procedures that reduce DA action result in a decrease in memory (Bernabeu et al., 1997). The same

pattern has been shown with D1 antagonists impairing memory when applied to the hippocampus (Morris et al., 2003). There is also evidence in humans that administration of L-DOPA, which enhances dopamine, is accompanied by subsequent improvement in memory (Knecht et al., 2004). It is known that disruption of COMT (enzyme which metabolizes dopamine) increases dopamine levels without affecting the levels of other monoamines (Gogos et al., 1998). Gene studies also show that carriers of the Met/Met genotype associated with lower COMT enzyme activity show better episodic memory (de Frias et al., 2004). In addition COMT inhibitor, can enhance various forms of memory, including episodic memory (Iudicello, Apud, Egan, Straub, Goldberg & Weinberger, 2004). Furthermore, there is evidence from an fMRI study suggesting that the human SN – a brain structure located in the midbrain containing dopaminergic neurons- and VTA can code absolute stimulus novelty and might contribute to enhancing learning in the context of novelty. In this study they reported SN/VTA activations in humans driven by novelty compared to other forms of stimulus salience such as rareness, negative emotional valence, or targetness of familiar stimuli (Düzel et al., 2009).

1.1.2.3.4.2 Norepinephrine

The locus coeruleus (LC) is a nucleus composed of mostly medium-size neurons located within the dorsal wall of the rostral pons in the lateral floor of the fourth ventricle that serves as the principal site for synthesis of norepinephrine (NE) in the brain (Jones & Moore, 1977).

The projections of the locus coeruleus spread throughout the central nervous system, with heavy innervation of the amygdala, brain stem, spinal cord, cerebellum, hypothalamus, thalamic relay nuclei, cingulate gyrus, hippocampus, striatum, basal telencephalon, and the cortex (Loizou, 1969).

The action of norepinephrine in each neuroanatomical region is determined by the expression patterns of the various adrenergic receptor subtypes ($\alpha_1, \alpha_2, \beta_1, \beta_2, \beta_3$). Noradrenergic system has been shown to interact with novelty processing and memory formation. Early studies in the 70s and 80s described an attenuation of perforant path-evoked potentials in the dentate gyrus of the hippocampus in aroused animals to be dependent on the activation of the noradrenergic nucleus LC (Dahl & Winson, 1985; Winson & Abzug, 1978). However, beta-receptor-dependent potentiation, not attenuation, has been repeatedly observed in anaesthetized animals and in brain slices (Klukowski & Harley, 1994). Sara in 1995 showed that novelty-seeking behaviour in mice is enhanced by idazoxan which increases noradrenaline release, and decreased with propranolol which blocks it (Sara, Dyon-Laurent, & Hervé, 1995). Complementary experiments have shown that noradrenergic neurons in the locus coeruleus fire in a bursts when the rat first encounters the novel object in the hole, and that the response habituates usually after a single exposure to the object (Sara, Vankov, & Hervé, 1994; Vankov, Hervé-Minvielle, & Sara, 1995). In 1997, Kitchigina and colleagues found a tonic increase in the DG population spike amplitude when the rat was placed in a novel holeboard environment, but this effect gradually disappeared with exposure. This increase was partly blocked in the presence of the β -noradenergic antagonist propranolol. Furthermore, phasic increase in spike amplitude when the rat encountered a

novel stimulus which lasted between 50 and 75 s and was not observed in presence of propranolol. These results suggest that activation of the noradrenergic system by the novel stimulus mediates this behaviour-dependent gating (Kitchigina, Vankov, Harley, & Sara, 1997).

In 2003, Straube and co-workers showed that distinct types of late-LTP in the DG depend on β -adrenergic receptor activation (Straube, Korz, Balschun & Frey, 2003). Another study by Straube and colleagues demonstrated that the novelty-induced LTP reinforcement was blocked when the protein synthesis inhibitor anisomycin or the β -adrenergic antagonist propranolol were applied intracerebroventricularly before exploration onset (Straube, Korz, Balschun & Frey, 2003).

Novelty effects and the P300 have been associated with the LC–NE system (Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010; McCarthy & Donchin, 1981; Nieuwenhuis, Aston-Jones, & Cohen, 2005; Wetzell, Schröger, & Widmann, 2013). Early studies reported that P300-like response disappeared in monkeys after LC lesion (Pineda, Foote, & Neville, 1989). There is also work showing P300 response correlations with pupil diameter (Murphy, Robertson, Balsters, & O'Connell, 2011), which is thought to be a proxy measure of locus coeruleus activation (Alnaes et al., 2014; Nieuwenhuis et al., 2005; Phillips, Szabadi, & Bradshaw, 2000). At the same time, LC is connected with the anterior cingulate cortex, the orbitofrontal cortex (OFC); (Aston-Jones & Cohen, 2005), and the prefrontal cortex (Sara, 2009). All of these regions are suggested to be sources of the novelty P300, supporting a role of the noradrenergic system in eliciting the novelty P300. The role of the LC-NE system in novelty and subsequent facilitatory

effects on behaviour is based on similarity of conditions eliciting facilitation and the novelty P300, and similar timing of the effects. For example, novelty is thought to be facilitating responses 100-200ms after stimulus presentation (Schomaker & Meeter, 2014), coinciding with the timing of the NE peak (Aston-Jones & Cohen, 2005; Nieuwenhuis et al., 2005). However, direct relationships between LC-NE system, novelty P300 and facilitatory effects have not been shown yet.

There is converging evidence from animal and human studies showing a fundamental role of the hippocampus in novelty detection. However mechanisms underlying remain unknown. In this thesis electrophysiological mechanisms of novelty detection in the human hippocampus will be studied.

1.1.2.3 Hippocampus and voluntary movement

From the late 1960s onwards, the relationship between hippocampus and movement has been subject to an ongoing debate and by extension the relationship between movement and memory processes. Nadel and colleagues showed that dorsal and ventral hippocampal lesions causes hyperactivity in novel situations in the rat most commonly observed in situations which are novel to the animal (open field, strange apparatus) or in which some significant element has been recently changed (Kimble, 1975; Nadel, 1968). There was also evidence arising suggesting that hyperactivity produced by median raphe lesion- or parachlorophenylalanine (PCPA) injection –which reduces levels of serotonin- is mediated specifically by the hippocampus in the rat. Aspiration of the anterodorsal hippocampus of adult male rats prior to median raphe lesions or PCPA

administration abolished the ability of both of these treatments to produce locomotor hyperactivity in animals (Jacobs, Trimbach, Eubanks, & Trulson, 1975).

Episodic memory and spatial navigation have been suggested to be intrinsically linked functions carried out by the hippocampus in a way that episodic memory needs spatial context to be encoded. Some authors even consider the role of the hippocampus in navigation to be memory (Eichenbaum, 2017). At the same time, spatial navigation obviously requires voluntary movement, which suggests a link between episodic memory and movement.

Memory studies in humans often include movements such as button presses, however the relationship between voluntary movements and memory encoding has not yet been investigated and little is known about how motor and memory systems interact. A possible relationship between the motor and memory systems is suggested by intracranial recordings from the human medial temporal lobe. In contexts not requiring explicit memory encoding, voluntary movements of the arm or tongue modulate neuronal firing rates in hippocampus (Halgren, 1991). Particularly, the largest amplitude of action potentials were when the patient moved his tongue and with skilled movements of the hand. Concurrently, other work showed hippocampal and surrounding cortex units responding to both observation and execution of actions. Interestingly, hippocampal and parahippocampal gyrus firing rates were shown to increase during whole hand execution, whole grasp and precision grip execution (Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010).

Furthermore, a type of eye movement, saccades, modulates hippocampal activity in both human (Andrillon, Nir, Cirelli, Tononi, & Fried, 2015; Hoffman et al., 2013) and non-human primates (Jutras, Fries, & Buffalo, 2013; Ringo, Sobotka, Diltz, & Bunce, 1994). Specifically, in non-human primates, saccadic eye movements during picture encoding evoke phase reset of theta oscillations, with post-saccade phase reliability predicting subsequent recognition (Jutras et al., 2013). In addition, the presence of a theta rhythm in the hippocampus during a movement seems to be more likely during discrete (e.g., reaching for an object) than continuous movements (e.g., running), as has been shown in primates (Isaacson & Pribram, 1975; Vanderwolf, Kramis, Gillespie, & Bland, 1975).

In humans, fMRI data suggests that visual exploration (eye movements) and hippocampal binding processes are inherently linked. The more gaze fixations -which implies more eye movements- during performance of a face processing task the stronger the hippocampal activation. This finding suggests that visual sampling predicts hippocampal activation (Liu, Shen, Olsen & Ryan, 2016).

There is also a study in humans describing memory as an active process that is intrinsically linked to behaviour showing that volitional control of a moving window, through which subjects studied objects and their locations, is beneficial for memory performance and is linked to a network that is centred in the hippocampus (Voss, Gonsalves, Federmeier, Tranel, & Cohen, 2011).

However, a relationship between action and episodic memory has only been demonstrated in relation to the enactment effect (Engelkamp & Cohen, 1991;

Engelkamp, Zimmer & Biegelmann, 1993; Zimmer, 2001), where the content of the memory is related with the movement. It remains unknown whether the memory of the movement can be dissociated from the effect of engaging the motor system on memory. This is one of the research questions investigated here in this thesis.

1.1.3 Norepinephrine and memory

The most commonly used approach to study the influence of NE on memory is to manipulate noradrenergic transmission before or after memory acquisition. The animal is tested at a later time point, when the effect of the drug has presumably dissipated. Using this approach, it has been demonstrated that NE interacts with other neuromodulators and stress hormones in the amygdala or the hippocampus, to promote long term memory (Mcgaugh & Roozendaal, 2009).

Early studies in rats found that post-trial injections of epinephrine administered shortly after inhibitory avoidance training exhibit inverted-U dose-response curves for effects on retention with relatively weak footshock. This means that low doses do not alter retention performance; moderate doses enhance and high doses impair later retention performance. Furthermore, a single dose of norepinephrine will enhance later retention of low footshock training and impair later retention of high footshock training (Gold & Buskirk, 1978, 1975, 1976a, 1976b; Gold, Buskirk, & Haycock, 1977).

The same authors showed a detrimental effect on memory retention of post-trial injections of norepinephrine (NE) in rats in high arousal context while in low arousal context norepinephrine can enhance memory. In this set of experiments, rats were

trained in a one-trial inhibitory (passive) avoidance task. A post-trial injection of NE enhanced retention of training with low footshock (i.e., low arousal) and impaired retention of training with high footshock (i.e., high arousal) 24 hours later (Gold & Van Buskirk, 1978). High levels of arousal -stressful events- result in transient increase in brain norepinephrine concentrations (reviewed in Glavin, 1985). Thus, norepinephrine injection after high arousal learning might saturate NE levels that can be beneficial for memory retention, turning in a detrimental effect on memory. Together, this evidence suggests that memory performance follows an inverted U shaped as a function of NE levels in the brain in a manner that reflects the Yerkes Dobson arousal curve (Yerkes & Dodson, 1908).

In addition, pharmacological studies suggest there is an opportunity time window when the noradrenergic system is engaged after learning experiences to reinforce long term memory. If an injection of β -receptor antagonist is applied immediately after the learning process, there is no effect in memory, while if the β -receptor antagonist is applied 2 hours after learning, the rat showed amnesia when tested 48 hours later (Sara, Rouillet, & Przybyslawski, 1999; Tronel, Feenstra, & Sara, 2004).

There is evidence showing that LC activity can enhance LTP. Pharmacological stimulation via glutamate injection in the LC (Klukowski & Harley, 1994) or electrical stimulation (Harley, 1991) in awake rats potentiates population spike amplitude in dentate gyrus in a long lasting way (>25 min), supporting the hypothesis that phasic activation of LC cells is likely to induce possibly long term potentiation of dentate gyrus throughput.

Other studies have related memory function with LC activation, particularly during retrieval. Sara and colleagues (1988) showed that low level stimulation in LC immediately before memory testing and 5 weeks after training in a linear maze for food reinforcement, alleviates forgetting. Animals made significantly less errors compared with the non-stimulated group (Sara & Devauges, 1988). A similar study reported facilitatory memory effects in rats that have forgotten a series of left–right turns in a maze via α -2 adrenoceptor agonist (idazoxan) administration (Sara & Devauges, 1989). Complementary pharmacological studies implicate the β -noradrenergic receptor in mediating this noradrenaline-induced retrieval facilitation (Devauges & Sara, 1991).

There is also a study in humans using resting-state functional connectivity to explore LC connectivity in two groups: healthy older and aMCI patients. They reported left LC-left parahippocampal gyrus (PHG) connectivity is associated with performance for both memory encoding and recall in healthy older people, this connectivity was reduced in aMCI patients (Jacobs et al., 2015).

Together this evidence suggests that the NE system is important for long-term memory consolidation, as described by Kety and coworkers (1971) when they presented a hypothesis that anticipated the important role of noradrenaline in LTP and memory processes (Kety, 1971).

1.1.3.1 NE system in emotional memory

Converging evidence implicated a role of the adrenergic system in consolidation of memory for emotionally significant experiences. Emotional arousal leads to activation

of the LC with the subsequent release of norepinephrine in the brain, resulting in enhanced memory performance. Previous studies have shown in rats that NE release increased by arousing stimulation -foot shock stimulation (Galvez, Mesches, & McGaugh, 1996) or immobilization and tail pinch (Ordway, Gambarana, & Frazer, 1988; Rainbow, Parsons, & Wolfe, 1984; Tanaka et al., 1991)- leads to the activation of adrenoreceptors of the complex of the amygdala serving as a functional regulation. These levels of norepinephrine are also related with memory performance in inhibitory avoidance paradigms. McIntyre and colleagues have shown a positive correlation of the levels of noradrenaline in the amygdala with retention performance 24 hours later (McIntyre, Hatfield, & McGaugh, 2002). Furthermore, infusion of β receptor antagonists in the amygdala produces amnesia in rats (Gallagher, Kapp, Musty, & Driscoll, 1977), while infusion of β receptor agonist enhanced memory consolidation (Ferry, Roozendaal, & McGaugh, 1999; Hatfield & McGaugh, 1999). There is also evidence that GABAergic agonist/antagonist modulates emotional memory by controlling levels of NE in the Amygdala. For instance, a $GABA_A$ receptor antagonist (picrotoxin) increases NE levels in the amygdala (Hatfield & McGaugh, 1999; McGaugh, 2004), while $GABA_A$ receptor agonist (muscimol) decreases the NE levels in the amygdala (Hatfield & McGaugh, 1999; McGaugh, 2004).

There is evidence from animal studies that injecting NE to various brain regions during encoding or shortly after leads to an enhancement of memory performance (McGaugh et al., 1993; van Stegeren, 2008). On the contrary, it is also known that blocking adrenergic β receptors prevents the increase of memory performance (Cahill &

McGaugh, 1996; McGaugh, 2004), even when this memory performance was artificially raised by agonistic injection (Liang, Juler, & McGaugh, 1986).

In humans, emotional arousal facilitated memory consolidation and this facilitation can be blocked by propranolol (β receptor antagonist) administration (Cahill, Prins, Weber, & McGaugh, 1994; LaBar & Cabeza, 2006; McGaugh, 2000, 2004). The administration of beta-blockers impairs memory of an emotionally arousing story but does not affect memory of a closely matched emotionally neutral story (Cahill et al., 1994). fMRI studies also show that amygdala activation during encoding of emotional stimuli is blocked by administration of β -adrenergic antagonist (Richardson, Strange, & Dolan, 2004; Strange, Hurlmann, & Dolan, 2003; van Stegeren et al., 2005).

There is also evidence that NE mediates the regulation of synaptic plasticity of the amygdala. Previous studies have shown LTP of cortical and thalamic inputs to Lateral Amygdala (LA) mediated by β adrenergic receptors (Huang, Martin & Kandel, 2000) and α_2 adrenoreceptors- lead to suppression of release of NE by negative feedback - impairing LTP at projections from the LA to the Basolateral Amygdala (BSA) (DeBock et al., 2003). NE modulates the suppression of GABAergic inhibition suggesting the ability of NE to gate LTP at glutamatergic synapses (McGaugh, Cahill & Roozendaal, 1996).

In summary, the release of NE during emotional events can modulate synaptic plasticity in the amygdala and hippocampal circuits to promote memory formation. Norepinephrine might serve adaptive behaviour by modulating memory for potentially threatening stimuli to be remembered when such stimuli are encountered in the future.

1.1.3.2 Norepinephrine and voluntary movements

An important function thought to be carried out by the LC is to coordinate the speed and efficiency of motor response to salient stimuli. This has a remarkable survival value in order to increase detection and elicit a fast response to stimuli (Berridge & Waterhouse, 2003). For example there is evidence showing that LC activity facilitates postural mechanisms, signal transmission to spinal interneurons, motoneurons and spinal reflex activity (Fung, Manzoni, & Chan, 1991; Pompeiano, Horn, & D'Ascanio, 1991), thus preparing for actions.

Clayton et al (2004) demonstrated LC neurons are phasically activated in close temporal relation to the behavioural response in a forced-choice task in monkeys. When LC activity was locked to the onset of the behavioural response (lever release), the LC response was more temporally constrained, and was not dependent on the correctness of the trial, the speed of response, nor on the anticipation of reward (Clayton, Rajkowski, Cohen, & Aston-Jones, 2004).

Kalwani et al (2014) showed that LC units responded to both the onset of the visual cue instructing the monkey to initiate the saccade (Go) and again after saccade onset, even when it was initiated erroneously in the presence of a stop signal. Many of these neurons did not respond to saccades made outside of the task context. In contrast, neither the appearance of the stop signal nor the successful withholding of the saccade elicited an LC response. They concluded LC phasic activation corresponded to the reward-driven decision to act, but not the reward- driven decision not to act.

Bouret and Richmond (2009) showed in a rewarded operant task, where monkeys were instructed to touch a bar after a go signal, that LC phasic activation is locked to the bar release (Go response) for the reward, to the go signal cue appearance on the screen and that this firing pattern was not affected by the reaction times (Bouret & Richmond, 2009). They later performed a similar experiment with 3 different conditions: (1) active trials where a cue indicating the size of the reward was presented and then a bar had to be released after the go signal cue, (2) passive trials where the cue was presented indicating reward size but no action were required (2s after the onset of the cue the reward was given) and (3) self-initiated trials where no cue was presented and touch and release of the bar was required to receive the reward. Phasic LC activation occurred in cued-active trials just before the action that preceded the feedback by a few milliseconds. In cued-passive trials, there was a small activation after the feedback announcing the imminent reward delivery. For the self-initiated trials there was LC activity with the initiation of the bar release, similar to cued-active trials. Interestingly, although a significant proportion of individual neurons displayed a firing modulation related to reward before the feedback in self-initiated trials, there was no modulation related to the reward size at the population level. Thus, the effects observed on individual neurons are not coherent enough to emerge at the level of the population (Bouret & Richmond, 2015).

Actions normally require a given amount of energetic resources to be mobilized which can vary depending on the nature of the movement. These resources include all the muscular, neuronal, and metabolic (such as oxygen, glucose, and ATP) components involved in the movement. Since LC activation is locked to the action and the decision

to act, it is possible that LC (NE release) is signalling this energy requirement to perform an action. There is a study that added another variable to account for effort (Varazzani, San-Galli, Gilardeau, & Bouret, 2015). At the beginning of the trial the cue indicated the size of the reward and also the effort required for the response. The response consisted in squeezing a bar with the level of effort indicated by the cue, once the force reached the correct level the monkey had to maintain the force until the reward came. The paradigm was designed looking for a clear double dissociation between two aspects of effort, cost and difficulty, and the activity of two major neuromodulatory systems, DA and NA (Varazzani et al., 2015). For dopaminergic neurons, located in the substantia nigra pars compacta (SNc unit), the response magnitude increased with the reward and decreased with the expected effort locked to the cue onset. Conversely, LC unit activation not only increased at the cue with reward expectation but also before and after the action onset, increasing with the effort. These results suggest SNc neurons are involved in coding value-based decision making e.g. monkeys decided to forgo trials with less reward and more effort required. On the other hand, LC and autonomic system is engaged when the animal faces the difficulty of producing the amount of force. This suggests a specific implication of NA neurons in mobilizing resources to energize behaviour and face the challenge at hand.

LC activity has been also shown to be triggered by action planning and/or motor action. That is previous evidence from single unit recordings in cats show that putative noradrenergic neurons of the LC change their firing rate before the beginning of a self-initiated motor act (Pavlenko & Kulichenko, 2003).

In summary there is evidence suggesting a strong relationship between LC phasic activation and voluntary movement. There are several studies showing LC phasic activation aligned to both the onset of the stimulus presentation and voluntary movement response (Bouret & Richmond, 2009; Clayton et al., 2004; Kalwani et al., 2014). Strikingly this LC response was shown to be better aligned to the movement compared to the stimuli presentation in (Clayton et al., 2004) and was not elicited either in the presence of a response inhibition cue, or with the successful withholding of the movement (Kalwani et al., 2014). Interestingly, this LC response is elicited regardless of speed of response (Bouret & Richmond, 2009; Bouret & Richmond, 2015; Clayton et al., 2004), correctness (Clayton et al., 2004; Kalwani et al., 2014) or reward expectation –LC fires with action even when the animal did not anticipate reward- (Bouret & Richmond, 2015; Clayton et al., 2004). Furthermore the anticipation of effort needed to perform an action has been also shown to modulate LC firing suggesting that LC is also signalling the energy requirements of the movement (Varazzani et al., 2015).

This together with the fact that this LC phasic response has been observed before the onset of the movement or with the onset of the stimuli presentation led to the suggestion that LC phasic response is driven by the outcome of a decision process and the commitment to act. Thus, NE release in motor circuits may promote synaptic throughput to facilitate behavioural responses once the decision has been made. But it is also possible that LC can be primarily involved in motor-related strategies in stimulus-response actions that do not call for high-level cognitive decision processes. It could also be possible that later components of the LC activation would produce NE liberation after motor circuits are already activated. This implies that the LC response triggered by

an action may serve functions in addition to facilitate the behavioural response such as memory function as suggested in (Clayton et al., 2004). This is one of the research questions that the present thesis will address.

In conclusion, there is evidence suggesting that emotion can modulate episodic memory via noradrenergic drive (see 1.1.3.1 NE system in emotional memory). There is also evidence that voluntary movements trigger LC activation and subsequently, noradrenaline release (see 1.1.3.2 Norepinephrine and voluntary movements). Together with the hypothesis raised in previous section (see 1.1.2.3 Hippocampus and voluntary movement) that voluntary movements can also modulate episodic memory, this thesis will investigate a movement-evoked memory enhancement and a possible interaction between emotion and voluntary movement during episodic memory encoding and its potential noradrenergic system involvement.

1.2 Neural code of memory

“Neurons that fire together, wire together” is a statement that encapsulates Hebb’s postulate. This postulate suggests that coordinated activity of a presynaptic terminal and postsynaptic cell would strengthen the synaptic connection between them, conversely uncoordinated activity between synaptic partners would weaken their synaptic connections (Hebbs, 1949). This early theory laid the foundation of what nowadays is known as Spike Timing Dependant Plasticity (STDP) (Markram, 2010) given by Long Term Potentiation (LTP) or Depression (LTD) processes. Hence, presynaptic firing shortly before postsynaptic firing of neurons cells leads to LTP, which according to Hebb’s postulate would be the coordinated activity; while postsynaptic activity before presynaptic activity leads to LTD which would refer to uncoordinated activity in Hebb’s postulate. Indeed, there is compelling data demonstrating LTP *in vivo*, showing that following the application of a tetanic stimulation there is a significant increase in the amplitude of excitatory postsynaptic potential out for about a year time. This results suggests that LTP may indeed be the mechanisms by which information at the synaptic level is stored across a lifetime (Abraham, Logan, Greenwood, & Dragunow, 2002).

This is not the only example in the brain in which coordinated timing of firing patterns of cells is decisive to code information. As has been introduced before (see 1.1.2.1.1 Place cells) place cells activity correlates highly with the location of the animal in the environment (McNaughton, Barnes, & O’Keefe, 1983; Müller, Stephan, Philippsen, & Steinmetz, 1987; O’Keefe & Dostrovsky, 1971; O’Keefe, 1976; Olton, Walker, & Gage, 1978). O’Keefe discovered an even more compressed spatial code within the

timing of the firing pattern of the place cells. The firing pattern of these cells provides a much higher spatial resolution than merely increase its firing rate at certain locations; it is also the phase of the population theta in which the place cell fires which localises the rat within the place field. This phenomenon is known as “Phase Precession” (O’Keefe & Recce, 1993).

Theta rhythms are low frequency sinusoidal waves between 4-12 Hz that occur in all hippocampal sub-regions during active exploration and rapid eye movement in rodents. High-amplitude theta is easily observed during locomotor behaviours in rodents (Colgin, 2013; Vanderwolf, 1969). These theta rhythms are periodically fluctuating waves of neuronal activity that can be observed using local field potential (LFP) recordings. These rhythms reflect the synchronized activity of large numbers of neurons because synchronous currents sum together to generate large-amplitude fluctuations in LFPs, whereas non-synchronized currents do not sum together and thus remain too small to be detected. These synchronous currents can be understood as generators of a certain rhythm measured in the LFP and have been located within -local generators- and outside -extrinsic generators- the hippocampal formation. The medial septum–diagonal band of Broca (MS-DBB) has been suggested to be a pacemaker for theta rhythms, since it was shown that hippocampal theta is abolished by septal lesions (Petsche, Stumpf, & Gogolak, 1962). However, there is more recent evidence that theta can be intrinsically being generated within the hippocampal structure CA3 (Buzsáki, 2002; Kocsis, Bragin, & Buzsáki, 1999; Konopacki, Bland, & Roth, 1987) and CA1 (Goutagny, Jackson, & Williams, 2009). This theta rhythm has been functionally related with learning and memory, synaptic plasticity, coordination of neuronal activity, active

sampling of sensory stimuli, among others (reviewed in Colgin, 2016). Interestingly, in human hippocampus this theta rhythm is thought to be less prominent -smaller in amplitude and duration- and typically identified at lower frequencies (Jacobs, 2013; Watrous, Lee, Izadi, & Gurkoff, 2013; Zhang & Jacobs, 2015).

O'Keefe and Recce (1993) described phase precession in the hippocampus and examine the relationship between the firing pattern of place cells recorded with tetrodes and the theta EEG signal measured by adding the signals from the tetrode. First, there is a specific bursting pattern of place cell firing while the rat is within and moving through the place field. Second, the bursting rate of each cell has a higher frequency than the corresponding EEG theta rhythm. Third, they observed the precession of this bursting pattern relative to the EEG theta waves. That is, they showed a phase shift backwards in the theta cycle as the rat advanced in the field, irrespective of the speed of the animal. This phase shift fitted better with a line with a negative slope against the position within the place field at the time of spiking than with the time of entering in the place field. Fourth, the onset of the bursting occurs at a constant point of the theta waves as the animal enters the field, meaning the afferent input to this cell must be timed to begin consistently in a certain phase. Fifth, the bell shape of the firing field and the tendency for the peak firing to occur in the middle of the phase shift. Finally, the confinement of the phase shift to 360 degrees or less meaning that the entering and exiting of the rat of the place field paces the EEG theta wave. These and related results on phase precession (Lenck-Santini & Holmes, 2008; Pastalkova, Itskov, Amarasingham, & Buzsáki, 2008; Skaggs & McNaughton, 1996) suggest that the hippocampus uses a code in which theta phase carries precise information about location within the place field.

1.2.1 Theta-gamma neural code

In addition to the theta rhythmic activity, there are also other rhythms present in the hippocampal LFP: Gamma rhythms have been recorded in the hippocampus during a variety of behaviours but they show lower amplitude than the theta rhythms (Buzsáki & Vanderwolf, 1983; Csicsvari, Jamieson, Wise, & Buzsáki, 2003). There is general consensus about gamma frequency range defined between 25 to 100 Hz, although there is literature that distinguish them in “slow gamma” (~25– 55 Hz) and “fast gamma” (~60–100 Hz). Slow gamma is thought to be driven by CA3 (Belluscio, Mizuseki, Schmidt, Kempter, & Buzsaki, 2012; Colgin et al., 2009; Kemere, Carr, Karlsson, & Frank, 2013; Schomburg et al., 2014) and couples activity in hippocampal sub-region CA1 to inputs from CA3. Memories are thought to be stored in and retrieved from the CA3 network (Brun et al., 2002; Nakazawa et al., 2002; Steffenach, Sloviter, Moser, & Moser, 2002; Treves & Rolls, 1992), thus a plausible hypothesis is that slow gamma promotes memory retrieval as suggested in (Colgin, 2016). By contrast fast gamma is thought to be entrained by inputs from MEC (Belluscio et al., 2012; Colgin et al., 2009; Kemere et al., 2013; Schomburg et al., 2014) which in turn is thought to process sensory information and transmit this information to the hippocampus (Canto, Wouterlood, & Witter, 2008). Therefore, one plausible function for fast gamma is the encoding of current sensory information in memory (Colgin, 2016).

To better understand the role of theta and gamma oscillations in cognition, it is necessary to understand the mechanisms underlying rhythmic activity. Studies using single unit and multi-unit recording show that rhythmic firing might be produced by

intrinsic firing patterns of excitatory principle cells or common input from a pacemaker. In the hippocampus, rhythmic firing can be seen as a result of the interactions between excitatory principle cells and inhibitory interneurons (Whittington, Traub, Kopell, Ermentrout, & Buhl, 2000). When excitatory principle cells or inhibitory interneurons activity occurs collectively, neurons fire together or are inhibited together, creating rhythmic firing patterns (Buzsáki, 2006). Excitatory principle cells activation leads to excitation of inhibitory interneurons which inhibit further excitation until this inhibition wears off, allowing excitatory neurons to fire again.

Different frequencies of rhythmic firing patterns (gamma or theta) depend on the rhythm of the inhibitory neurons which the excitatory principle cells are interacting with. Whereas gamma rhythmic firing occurs through the interaction of excitatory principle cells and fast basket cell inhibitory interneurons (Banks, White, & Pearce, 2000; Bartos, Vida, & Jonas, 2007; Cells, 1994; Mann & Paulsen, 2005; Penttonen et al., 1998; Whittington et al., 2000) acting on fast Gamma-aminobutyric acid (GABA_A) receptors (Banks et al., 2000; Soltesz & Deschenes, 1993; Traub, Whittington, Colling, Buzsaki, & Jefferys, 1996; Whittington et al., 2000), theta rhythmic firing occurs through the interaction of excitatory principle cells and slow stellate cell inhibitory interneurons (Dickson et al., 2000; Rotstein & Pervouchine, 2005) acting on slow GABA_A receptors (Banks et al., 2000; Buzsáki, 2002; Cobb, Buhl, Halasy, Paulsen, & Somogyi, 1995; Soltesz & Deschenes, 1993).

In addition, rhythmic firing at different frequencies can multiplex such that faster rhythms are modulated by and nested within slower rhythms (Bragin et al., 1995;

Chrobak & Buzsáki, 1998; Csicsvari et al., 2003; Penttonen et al., 1998; Soltesz & Deschenes, 1993). Although there is little evidence of the mechanism responsible for nesting of gamma rhythms within theta rhythms, it has been speculated that theta rhythms modulate gamma rhythms through the action of inhibitory interneurons (Bragin et al., 1995). The rhythmic firing of inhibitory interneurons at a theta frequency provides a depolarizing and hyperpolarizing current that activates and deactivates inhibitory interneurons firing at a gamma frequency. Supporting this idea, there is evidence showing that inhibitory interneurons acting on slow GABA_A receptors can also inhibit the activity of inhibitory interneurons acting on fast GABA_A receptors (Banks et al., 2000). This results in the activity of slow inhibitory interneurons inhibiting fast inhibitory interneurons that cause gamma rhythms. Therefore, theta rhythms can modulate gamma rhythms providing a possible mechanism for the nesting of gamma rhythms within theta rhythms.

Different rhythmic patterns in theta and gamma frequency bands are thought to interact with each other within and between brain regions during cognitive function representing a code in the brain. Firing patterns of different place cells firing in different theta phases can be recorded simultaneously and understood as a multipart message multiplexing spatial information, (reviewed in Lisman & Jensen, 2013).

There is evidence suggesting that CA1 place cells fire at a preferred phase of the faster gamma oscillations meaning that firing tends to occur at a particular preferred gamma phase (Senior, Huxter, Allen, Neill, & Csicsvari, 2008). Interestingly, all place cells that fire in a place field fired at a preferred phase in the gamma cycle, and at a population

level this preferred phase was more consistent –more place cells showing it- when the rat was inside the place field compared with when it was outside. They end up concluding that cells that fire at the trough of the population gamma cycle -Topyr cell- firing is organized in sequences which occur across subsequent gamma cycles nested within each theta cycle. This activation is supposed to represent movement trajectories. Conversely cells that fire at the rising phase of the population gamma cycle -Rispyr cells- fire in synchronized gamma discharges without temporal sequences. They presumably encode a representation of location. In summary, this study provides evidence of a theta-gamma code within CA1. Topyr cells fire at preferred phases of the gamma LFP signal which in turn are nested within the theta cycle arranged in sequences representing movement trajectories.

Another study described how different place cells fire in different phases of theta one after the other, and in an order corresponding to the place field of subsequent positions ahead. Thus, such activity sweeps represent positions along the path ahead of the animal. This implies, as the animal moves, place cells of future locations are firing in order at different phases of the theta cycle. This shows at the population level that phase precession implies compressed sequences of place cell activity emerging during each theta cycle (Gupta, van der Meer, Touretzky, & Redish, 2012). Furthermore, sweeps seem to be time compressed, whereas the rat might take 300 ms to move between positions a and b, cells representing these positions fire 30 ms apart during a sweep (Skaggs, McNaughton, Wilson, & Barnes, 1996). This time compression often predicts subsequent position (Battaglia, Sutherland, & McNaughton, 2004). Codes that take theta phase into account allowed the rat's position to be predicted with an accuracy of

about 3 cm, while codes that did not use theta phase had less accuracy (Harris, Csicsvari, Hirase, Dragoi, & Buzsáki, 2003; Jensen & Lisman, 2000). Place cells that have nearly identical place fields tend to fire in the same gamma cycle (Dragoi & Buzsáki, 2006). This converging evidence suggests that there is a theta-gamma code in the hippocampus to represent ordered multi-item messages. Accordingly, these cell populations can be viewed as gamma-theta multiplexors (Figure 5).

Figure 5. Simplified model of a theta-gamma code for place cells populations based on the model by (Lisman & Jensen, 2013). Place cell populations work as a theta-gamma multiplexor in which non-overlapping assemblies of cells are active in different gamma cycles at different theta phases. This is based on the idea that (1) during a given theta cycle place cells tends to fire at a preferred theta phase (O'Keefe & Recce, 1993; Skaggs et al., 1996) and (2) during an individual theta cycle different place cells fire in a temporal sequence (sweeps) because the firing order corresponds to the cells' place field centers along the track (Gupta et al., 2012). If a place cell fires at a particular phase during a theta cycle (i.e., in a particular gamma cycle), other place cells representing different information presumably fire at other theta phases, collectively forming a multipart message.

Together this converging evidence suggest not only the existence of a theta-gamma code in the brain, but also that gamma activity in the LFP signal can capture the contribution of single unit activity to the measured signal.

1.2.2 Theta gamma code in memory

Models on the functional role of gamma and theta rhythms in episodic memory have proposed that the hippocampus is suggested to bind information from diverse cortical regions into episodic memory representations via modifying synaptic strength between input neurons and hippocampal neurons through long-term potentiation (Nyhus & Curran, 2010).

Potentially, gamma in the cortex can bind perceptual features and in the hippocampus bind perceptual and contextual information from different brain regions into episodic representations. Theta can order these episodic representations in time. Based on time restrictions, gamma is more likely to elicit Spike Timing Dependant Plasticity (STDP) than theta. On the one hand pre-synaptic firing, which is supposed to be a slow process (~20ms), must occur prior to postsynaptic firing which conversely is supposed to be a faster process (~1ms). On the other hand, it has been suggested that gamma oscillation are important for STDP to occur. It is known that excitatory principle cells are more likely to fire at positive peaks of neural oscillations, given that LFP signals are thought to represent mostly neuronal input activity, the pattern of inputs of the gamma rhythms (25-100Hz) represents adequate timing for STDP to occur (Axmacher, Mormann, Fernández, & Elger, 2006; Nyhus & Curran, 2010).

Conversely, theta oscillations have been suggested to modulate LTP. This is based on the idea that the positive peak of a theta LFP is a consequence of depolarization. Depolarization would lead to the opening of NMDA channels causing calcium influx and consequently initiating the cascade of molecular processes for synaptic modification and memory formation (Huerta & Lisman, 1995). It has also been shown that stimulating at the theta frequency facilitates LTP in the DG (Greenstein, Pavlides, & Winson, 1988) and in CA1 neurons (Gordon, 1986; Larson, Wong, & Lynch, 1986; Rose & Dunwiddie, 1986) in the hippocampus. Furthermore stimulation coinciding with a positive peak of the theta cycle can induce LTP in DG (Pavlides, Greenstein, Grudman, & Winson, 1988) and CA1 neurons (Hölscher, Anwyl, & Rowan, 1997; Huerta & Lisman, 1995; Hyman, Wyble, Goyal, & Rossi, 2003) while no effect or depotentiation of previously potentiated synapses occurs when stimulating at the trough of the theta oscillation. These results suggest that the firing of neurons at the peak of the theta oscillation is optimal for LTP.

This model also suggests that there is a theta/gamma code model for episodic memory in which LTP leads to phase precession. Animal study show that when the animal enters a place field, the phase of theta oscillations is reset, indicating that the place cell is firing at the peak of the theta oscillation when LTP is most likely to occur (Buzsáki, 2002; Hölscher et al., 1997; Huerta & Lisman, 1995; Pavlides et al., 1988). Thus, during learning, a phase reset is observed in the firing of the place cell coincident with the peaks of the theta cycle which can facilitate LTP, plasticity mechanism which in turn it is suggested to led phase precession observed after learning (Axmacher et al., 2006).

Evidence from rodents suggests that theta/gamma coupling could be functionally important for long-term memory processes (Tort, Komorowski, Manns, Kopell, & Eichenbaum, 2009). In this study, as learning of the association between context and food reward location progressed, the animals showed an increase in cross-frequency coupling which the strength of coupling predicting the probability of correct choice. Shirvalkar, Rapp, & Shapiro, (2010) showed that changes to hippocampal theta-gamma comodulation predict memory for recent spatial episodes, suggesting that theta-gamma coupling in the rat hippocampus enables the recall of stored information.

Theta-gamma coupling during working memory has been observed in humans in the hippocampus (Maris, van Vugt, & Kahana, 2011). Axmacher and colleagues reported that theta phase modulates gamma power during working memory retention and furthermore that the strength of the coupling correlates with working memory performance (Axmacher, Henseler, Jensen, Weinreich, Elger & Fell 2010). Several lines of studies suggests a model in which the number of gamma cycles within a theta cycle accounts for the working memory span (Jensen & Lisman, 1998; Koene & Hasselmo, 2007; Lisman & Idiart, 1995).

Similar lines of research have found items in different sequence positions exhibit greater gamma power along distinct phases of a theta oscillation and show that this segregation is related to successful temporal order memory using MEG in humans. In this study the main finding was that successful sequence encoding is accompanied by a theta–gamma phase coding mechanism, whereby gamma power associated with each sequential item is biased toward a distinct, consecutive phase of an underlying theta oscillation. This

was found for two clusters at sensor level. Left lateral and posterior, a source reconstruction showed hippocampal, parahippocampal gyrus and fusiform activations as possible sources for the sensor level clusters (Heusser, Poeppel, Ezzyat & Davachi, 2016). Therefore they show theta–gamma PAC and more specifically, theta phase coding, support object sequence memory.

These correlations of oscillatory properties with memory states and with memory performance support a functional role of theta and gamma rhythms and their interaction in episodic memory.

1.2.3 Neural code of novelty in the hippocampus: Theta and Gamma rhythms

Theta-related activity in the hippocampal formation supports spatial memory and novelty detection. Lever and colleagues reported that the preferred theta phase of firing of CA1 principal cells, shifts to a later phase of theta in response to novelty that is likely to be closer to the pyramidal-layer theta peak. This shift correlated with plasticity in the CA1 place cell representation (Lever et al., 2010).

The medial septum is known to set the pace of hippocampal formation theta and provides both GABAergic and cholinergic inputs (Buzsáki, 2002). Increases in cholinergic input to the hippocampus, as seen during exploration of a novel environment (Giovannini et al., 2001; Thiel, Huston, & Schwarting, 1998), result in a reduction of hippocampal theta frequency (Givens & Olton, 1995). Environmental novelty also provokes a reduction in hippocampal theta frequency which return to prior frequency with increasing familiarity showing an habituation pattern (Jeewajee, Lever,

Burton, O'Keefe, & Burgess, 2008). The authors conclude the GABAergic input sets the baseline theta frequency during motion, with increased cholinergic input mediating a reduction in overall frequency in response to novelty.

Studies in intracranial human recordings have explored unexpected processing in the hippocampus. Axmacher et al (2010) found the most pronounced difference between processing of unexpected and expected items in the hippocampus to be an early (200–400 ms) increase and a later (500–1400 ms) decrease of theta band activity, and an increase between 500–700 ms and 1000–1100 ms in the high gamma (70–90 Hz) frequency range. In addition, hippocampal ERPs show an early hippocampal component (peaking at 187 ms).

Similar studies in humans reported that associative prediction violations elicit increased low-frequency power (in the slow-theta range) in the hippocampus. They also observed an early onset of this increase in low frequency power after the moment of violation, and that changes in low-frequency power are not present in adjacent perirhinal cortex (Chen et al., 2013).

This evidence suggests that theta and gamma rhythms mediate novelty response in the hippocampus. However the oscillatory mechanisms underlying unexpected processing remain poorly explored in humans. In an attempt to give more insight about the role of theta and gamma oscillations during novelty processing, in this thesis oscillatory responses are going to be studied in the human hippocampus using an oddball task.

1.2.4 Theta and Gamma rhythms along the longitudinal axis of the hippocampus

A model in which functional long-axis gradients are superimposed on discrete functional domains has been suggested in (Strange, Witter, Lein & Moser, 2014). On the one hand, behavioural lesion in the hippocampus, electrophysiological recording and intrinsic-connectivity analyses suggest that there is a demarcated one third ventral division in the hippocampus, on the other hand, extrinsic connectivity, receptor expression and place field size suggest gradual changes along the hippocampus (gradients) while gene expression studies indicate that there are three sharply demarcated portions of the hippocampus.

Differences between dorsal and ventral hippocampus in spatial processing have been described in the literature. Particularly, initial data indicated that there are less place cells in ventral compared with dorsal hippocampus (CA1) and that ventral place cells showed lower spatial selectivity (Jung, Wiener, & McNaughton, 1994). More recent data reported that the relative size of place fields in area CA3 decreases almost linearly with position from the ventral hippocampal pole - where place fields are ~10 metres - to the dorsal pole -where place field size approaches 1 metre- (Kjelstrup et al., 2008). Subsequently, Royer and colleagues explored differences between dorsal and ventral CA3 electrophysiological properties in rats. They found that dorsal CA3 neurons had well defined single and compact place fields with high information content and spatial stability while this was only exceptionally observed in the ventral CA3. Instead, ventral CA3 neurons fired at multiple locations with interruption of activity between them with larger spatial coverage and significantly lower values of spatial information content

(Royer, Sirota, Patel & Buzsáki, 2010). This data is in line with the growing scale of grids toward the ventral hippocampus showing lower scale in dorsal MEC compared to ventral locations (Hafting et al., 2008, 2005). Changes in visual spatial processing along the long axis of the entorhinal cortex (EC) have been also recently described using electrophysiology data from non-human primates. Killian and colleagues found grid-like cell properties in the posterior EC during visual processing. The study showed that spatial scale varied as a function of distance from the rhinal sulcus (which is equivalent to the dorsomedial-to-ventrolateral axis in the rodent medial EC), suggesting that spatial scale may also vary along the primate hippocampal long axis (Killian, Jutras, & Buffalo, 2012). These findings support the hypothesis that neurons at different septo-temporal levels simultaneously represent the same environment with different spatial resolution suggested by (Jung et al., 1994; Kjelstrup et al., 2008; Maurer, Vanrhoads, Sutherland, Lipa, & McNaughton, 2005; McNaughton, Battaglia, Jensen, Moser, & Moser, 2006; Moser, Kropff, & Moser, 2008).

Royer and co-workers found that theta power was significantly lower in the ventral compared to the dorsal hippocampus in rats foraging in three different testing apparatuses. However, when present, ventral CA3 theta was temporally coordinated with theta derived from the dorsal hippocampus, as shown by both the distinct coherence peak in the theta band and the significant phase modulation of ventral gamma power by dorsal theta oscillations. While dorsal CA3 place cells and interneurons showed strongly rhythmic spike autocorrelograms at theta frequency, rhythmicity of ventral CA3 pyramidal cells and interneurons was less pronounced. Although the fraction of theta-rhythmic neurons in ventral CA3 was robustly lower than in dorsal

CA3, these theta-rhythmic ventral CA3 neurons also showed phase precession but with slower rate when compared to dorsal. In summary, they found a strong reduction of theta LFP power and a small proportion of theta-rhythmic neurons in the ventral compared to the dorsal CA3 neurons. Although, when this ventral theta rhythm exists, ventral theta coherence with dorsal CA3 neurons is observed, ventral theta phase modulates dorsal gamma amplitude and less ventral precession rate is observed compared to dorsal neurons (Royer, Sirota, Patel, & Buzsáki, 2010).

Sabolek and colleagues showed that theta and gamma coherence decreases along the septotemporal axis of the hippocampus during REM sleep in rat CA1 and DG sites. On the one hand, theta coherence decreases along the long axis of the hippocampus (from dorsal to ventral) larger than expected based on the fact that this portion of the hippocampus receives projections from the same band of the entorhinal cortex. On the other hand, this theta coherence is higher between homotopic regions (e.g. CA1-CA1) across hemispheres compared to homotopic regions within the same hemisphere. The latter result suggests that theta varies as a function of anatomical connectivity rather than physical distance and suggests a prominent influence of the bilateral projections from CA3 and mossy cells on theta current generation and theta coherence during REM sleep. They also show a dramatic gamma coherence drop along the long axis as a function of distance to septal portions. These results again suggest functional variability along the long axis of the hippocampus. At the same time, this can have implications on the understanding of the extracellular inputs current flows in the hippocampus recorded as theta and gamma (Sabolek et al., 2009). Interestingly, a similar drop in theta coherence has also been observed in human intracranial recordings during baseline

periods between head and body hippocampal areas (Staresina, Fell, Do Lam, Axmacher, & Henson, 2012). (Note that transition from hippocampal head to body can be defined taking the uncal apex as a landmark (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013))

Another study was performed providing results of gamma and theta coherence along the long axis of the hippocampus in rodents extending behavioural correlates not only for REM sleep but also for locomotion during maze running, following acute treatment with a theta-inducing cholinomimetic (physostigmine) and for comparison during slow-wave sleep in rats. They demonstrate that the general pattern of theta coherence across the septotemporal axis, while varying systematically (decreasing from dorsal to ventral), does not change in relation to gross changes in sensory input or overt behaviour. Furthermore, they report that theta modulation of gamma at all sites is similar during locomotor activity and REM sleep; however, the coupling of theta to gamma was significantly reduced during physostigmine-induced theta in both CA1 and the DG (Penley et al., 2012). Together, these results suggest that theta and gamma coherence decrease along the long axis from dorsal to ventral sites of the hippocampal formation. This pattern does not change in relation to sensory input or overt behaviour, while different parts of the hippocampus exhibit different theta and gamma power patterns depending on different behavioural states.

Moreover, Bullock and colleagues (1990) found that both the amplitude and phase of theta waves in rodents change as a function of depth (i.e., different layers), whereas in the same layers they are robustly similar along the long axis of the hippocampus

(Bullock, Buzsáki, & McClune, 1990). Conversely, there are several studies suggesting that there are changes in phase and amplitude within CA1 layers of the hippocampus along the long axis (Lubenov & Siapas, 2009; Patel, Fujisawa, Berényi, Royer, & Buzsáki, 2012).

Lubenov and Siapas (2009) demonstrated a consistent travelling wave pattern in the CA1 pyramidal cell layer. Theta oscillations in area CA1 are travelling waves that propagate roughly along the septotemporal axis of the hippocampus in freely moving rats. They only recorded limited distances from dorsal to ventral hippocampus and they hypothesized a full cycle (~360 degrees) phase shift from septal to temporal poles (Lubenov & Siapas, 2009).

Subsequently, Patel and colleagues in 2012 showed that theta waves were phase shifted by approximately a half cycle (180 degrees) between the septal and ventral sites in CA1. In addition, they showed that coherence of theta waves was relatively higher between septal and intermediate sites, than between septal and ventral sites. Moreover, a group analysis confirmed that the frequency of theta oscillations remained the same along the entire septo-temporal axis but differed significantly between REM sleep and maze behaviour (Patel et al., 2012).

This theta phase shift along the long axis has been also demonstrated in humans, Zhang and colleagues showed theta phase shifted monotonically with distance along the longitudinal axis of the hippocampus (Zhang & Jacobs, 2015). This finding suggests that different phases can be coded by different parts of the hippocampus. At the same time, this phase shift facilitates a phase code for integrating incoming information.

There are different oscillator theories generating this theta shift pattern along the long axis of the hippocampus. The first possibility is that this phase shift is produced by a septal single rhythm generator and the delays emerge due to the propagation velocity of septo-hippocampal afferents. This is argued to be unlikely. First, it would require precisely tuned delays in multiple collaterals of septal afferents to the different hippocampal regions that coincides with entorhinal inputs. Second, the frequency of theta oscillations depends primarily on the GABAergic neurons of the medial septal area (Lee, Chrobak, Sik, Wiley, & Buzsáki, 1994; Yoder & Pang, 2005), and the conduction velocities of thickly myelinated septo-hippocampal GABAergic neurons (Freund & Antal, 1988) are an order of magnitude faster than the propagation velocity of theta waves (Bilkey & Goddard, 1985). Third, the different septo-temporal segments of the hippocampus are not innervated by axons of the same septal neurons (Gage, Björklund, & Stenevi, 1983). Furthermore, the single oscillator model predicts a correlation between temporal frequency and propagation speed while a model of weak coupled oscillators predicts no such relation. Because conduction delays are fixed between the single oscillators (medial septum) connected with the long axis of the hippocampus, propagation speed should be constant regardless of the frequency. Zhang & Jacobs, (2015) observed a significant positive correlation between temporal frequency and propagation speed supporting the weak coupled intra-hippocampal and matched entorhinal cortex oscillator's model. This model is also supported by the fact that CA3 can generate theta oscillations with similar time delays (Kocsis et al., 1999; Konopacki et al., 1987; Miles, Traub, & Wong, 1988). In addition, place cell frequency decreases along the long axis of the hippocampus from posterior to anterior portions (Jung et al., 1994; Kjelstrup et al., 2008; Maurer et al., 2005; Royer, Sirota, Patel, &

Buzsáki, 2010) and theta oscillating cell groups are coupled by delays (Caroline Geisler, Robbe, Zugaro, Sirota, & Buzsáki, 2007). Similarly, the oscillation frequencies of medial entorhinal cortex neurons decrease progressively in the dorso-ventral direction (Giocomo, Zilli, Fransén, & Hasselmo, 2007), providing a frequency match between corresponding entorhinal and hippocampal neurons.

Together, there is converging evidence suggesting that there are travelling waves in CA1 in rodents (Lubenov & Siapas, 2009; Patel et al., 2012) and human (Zhang & Jacobs, 2015). A feasible model for generating these traveling waves in CA1 consists of weak coupled oscillators in CA3 matched with entorhinal cortex activity. Together with the continuous increase in the size of a CA3 place fields in the septal to temporal direction (Jung et al., 1994; Kjelstrup et al., 2008; Sabolek et al., 2009), this suggests that traveling waves can cause place cells to activate in order of increasing field size: septal cells with small place fields activate first, followed by temporal place cells with larger place fields. If this is the case, the hippocampus first represents specific information about the current location and later, as theta moves through space, it represents coarser spatial information.

In summary, studies have shown functional and electrophysiological differences along the long axis of the hippocampus. Two patterns of functional organization appear to be superimposed on the hippocampal long axis: gradual and discrete transitions reviewed in (Strange, Witter, Lein & Moser, 2014) together with genetic and connectivity differences. Despite these differences it is still a matter of debate whether there is a

functional integration or segregation along the long axis of the hippocampus during novelty processing.

1.2.4.1 Theta and Gamma rhythms along the long axis during novelty processing

The observation of two superimposed patterns of functional organization along the long axis of the hippocampus (Strange, Witter, Lein & Moser, 2014) suggests that there might be also electrophysiological changes in expectancy processing. However, the study of electrophysiological correlates along the long axis of the hippocampus during novelty processing remains to be understood.

Penley and co-workers described how theta and gamma power increases in novel spaces in both CA1 and DG in rats. This pattern was linked to successful encoding and subsequent retention of memories. Furthermore, theta and gamma coherence was found to increase along the long axis of CA1 but to decrease along the long axis of the DG (between distant electrode pairs septal to temporal). Despite evidence in rats showing theta and gamma coherence decreasing along the long axis in CA1 (Penley et al., 2012; Sabolek et al., 2009), these results suggest that there might be significant shifts in the afferent inputs from CA3 and entorhinal cortex to CA1 and DG across the long axis of the hippocampus during novelty processing. Thus, the theta and gamma input to CA1 receives and conveys a more coherent message during novelty processing that can may contribute to successful encoding of novel stimuli (Penley et al., 2013).

There is little known about oscillatory responses in humans along the long axis of the hippocampus during unexpectancy processing. To our knowledge, only one study have

compared responses between anterior and posterior hippocampal theta responses in humans during an incidental 1-back task (Chen, Dastjerdi, Foster, LaRocque, Rauschecker, Parvizi & Wagner, 2013). They showed that associative prediction violations elicited increased slow-theta power for mismatch compared to repeated items during the 0–500ms post-stimulus onset window when analyses were restricted to anterior hippocampal electrodes in all patients. Conversely, hippocampal power in these comparisons was not significant when analyses were restricted to posterior hippocampal electrodes. However, since only four participants were reported, it cannot be inferred that the prediction violation effects were selective to anterior electrodes.

Therefore, based on previous evidence it is still an open question whether different parts of the hippocampus along the long axis are functionally integrated or segregated during novelty processing function.

1.3 Overview of the thesis

As introduced in this chapter, a number of factors can influence episodic memory: novelty emotion and voluntary movement among others. However, the mechanisms underlying these influences remain poorly understood, particularly in humans. This thesis will address several mechanisms for enhanced memory encoding in humans. There are two experimental chapters. In the first (Chapter 3) the relationship between voluntary movements and memory and the mechanisms underlying will be investigated. In the second Chapter 4 (subdivided in Chapter 4a, 4b and 4c) electrophysiological correlates of novelty processing will be studied along the long axis of the hippocampus.

In the current Chapter, the multiple memory systems of the brain have been introduced, focusing on role of human hippocampus in episodic memory, navigation, novelty detection and voluntary movements. The roles of theta and gamma oscillations in memory, in novelty detection have also been reviewed as well as differences along the longitudinal axis of the hippocampus.

In Chapter 2, a general overview of different methods used in the experiments in this thesis will be described. Chapter 2 introduces Functional Magnetic Resonance Imaging (fMRI) and methods that can be use with this technique for accounting functional connectivity such as Physiological Interaction (PPI). Brainstem imaging methods will also be discussed as well as a method used to ascribe cognitive function with pupillary responses. Human intracranial recordings in epileptic patients measuring Local Field Potentials will be introduced as well as different analysis approaches, such as Event

Related Potential analyses and Cross Frequency Coupling (CFC) measures for the study of different oscillations present in the LFP signal.

Chapter 3 investigates, over a series of experiments, a voluntary movement-induced episodic memory enhancement and elucidates the neural mechanisms underlying. Specifically, behavioural experiments, fMRI and pupilometry, will be used to test the noradrenergic involvement of the observed action-induced memory enhancement.

Chapter 4 offers a comprehensive account of human hippocampal electrophysiology responses to novelty. In Chapter 4a, iEEG recordings of epileptic patients are going to be used to study the Event Related Potential components of the LFP signal in different portions of the hippocampal longitudinal axis: Hippocampal Head (HH), Hippocampal Body (HB) and Hippocampal Tail (HT) in order to investigate activity commonly evoked by novel stimuli.

In Chapter 4b, oscillatory responses along the long-axis of the hippocampus during novelty processing are going to be described. Systematic evaluation of gamma and theta frequencies along the long axis of the hippocampus will address the importance of those frequencies in novelty processing. For doing so, time frequency, imaginary coherence (iCoh), phase locking value (PLV), peak frequency analysis and CFC measures will be applied.

In Chapter 4c, using the same iEEG recordings, theta and alpha traveling waves along the long-axis of the human hippocampus showing different phases in different portions of the longitudinal axis are going to be presented. The frequency specificity,

directionality along the long axis and a possible modulation with novelty of the travelling wave pattern will be investigated. Conclusions of the experimental findings in this thesis are presented in Chapter 5.

Chapter 2

Methods overview

2.1 Ascribing cognitive function with Functional Magnetic Resonance Imaging (fMRI)

This Functional Magnetic Resonance Imaging (fMRI) is a non-invasive functional neuroimaging technique, among other functional techniques, that has made possible the identification of large scale activation patterns associated with high order cognitive processes. In the recent past we have witnessed an explosion in the number of published papers using this technique to address the neural mechanisms underlying cognitive process. In task-dependent fMRI, neural activity is measured through changes in blood oxygenation caused by the cerebral response to the stimulus-dependent neural firing. This activity is manifested in the form of changes in the grey matter contrast across the T2*-weighted echo-planar images that is known to be directly proportional to the underlying neural activity. The most common form of fMRI uses the blood-oxygen-level dependent (BOLD) contrast, as discovered by (Kwong et al., 1992; Ogawa, Lee, & Kay, 1990). Neurons do not have internal reserves of energy in the form of oxygen, so their firing causes a need for more energy to be brought in quickly. Through a process called the hemodynamic response, the local blood supply releases oxygen to those neurons at a greater rate than to inactive neurons. This in turn causes a change in the relative levels of oxyhemoglobin and deoxyhemoglobin (oxygenated or deoxygenated blood) that can be detected on the basis of their differential magnetic susceptibility. The temporal resolution of the hemodynamic measure is somewhat limited relative to brain monitoring technology that may provide more direct measures of neural activity such as EEG or MEG, but is capable of capturing brain function at far superior spatial resolutions. The temporal resolution of fMRI is defined by the relatively slow delay

time of the hemodynamic response which can lag behind the stimulus onset for between 3-8 seconds. A second potential problem relates to the ability of the technique to resolve events closely spaced in time, determined to some extent by the repetition time (TR) – time between contiguous slices acquired used for the sequences.

Most common analysis in fMRI involves comparisons between conditions within a task, involving statistical contrasts between the blood flow of a target task and a reference task. The resulting activation maps, exhibiting areas that pass statistical significance represent the relative increase in activity in one condition over another, this subtraction method can lead to a problem called “the pure insertion assumption” discussed in (Friston et al., 1996). This assumption asserts that there are no interactions among the cognitive components of a task. There are several ways described in the literature to overcome this problem. First is the use of “the cognitive conjunction” analysis suggested by Price & Friston (1997) where the common activity can be modelled and isolated in independent comparisons. While cognitive subtraction studies are designed such that a pair of tasks differs only by the processing component(s) of interest, cognitive conjunction studies are designed such that two or more distinct task pairs each share a common processing difference. Another solution would be the use of “parametric designs”. This type of designs allows characterizing the effect of a monotonic change in task parameter instead of testing a main effect by a subtraction of activations. Factorial designs allow interactions (“difference of the differences”) to be assessed. The use of “event related fMRI designs allows mixing different conditions (not being presented in blocks) in which, the presentation is randomized, and the time between stimuli can vary and allows sorting of trials into separate bins according to

cognitive performance and relating brain activity to these differences in performance. In Chapter 3, an event related factorial design will be presented.

All these approaches can be used to identify brain regions related to certain cognitive functions but do not give information about how different brain regions are functionally related and how they interact during task performance. For this purpose there are “network analyses” that can be performed with fMRI. These methods provide interregional correlations of brain activity between or within subjects. The integration within and between functionally specialized areas may be mediated by “functional” or “effective” connectivity (FC and EC). These two terms refer to temporal correlations between remote neurophysiological events and the influence one neural system exerts over another. Functional connectivity measures are typically associative in terms of their not specifying a direction of influence.

Physiological Interaction (PPI): is a technique based on extensions to statistical models of factorial designs, occupying a middle ground between models of functional and effective connectivity which are realized as models representing the relationship between connectivity and task contributions (Friston et al., 1997). PPI's are regression models, and a direction of influence is thus pre-specified based on investigator hypotheses. These are a somewhat limited model of EC because they commonly involve one source region and one experimental factor. The interaction between the source region and experimental context is usually interpreted in two ways (Figure 6): 1) in demonstrating how the contribution of one region to another is altered by the experimental context or task, or 2) as an example of how an area's response to an

experimental context is modulated by input from another region as can be seen in the following figure taken from (Friston et al., 2011).

Figure 6. Possible interpretations of a PPI analysis. A. How the contribution of one region to another is altered by the experimental context or task. B. How an area's response to an experimental context is modulated by input from another region. Figure taken from (Friston et al., 2011)

PPI estimates the degree to which activity in one area can be predicted on the basis of activity in another and can be understood in terms of quantifying the contribution of region 2 to region 1. Psychophysiological interactions offer a useful way to make inference about functional integration using context-sensitive contributions. In Chapter 3, results of a PPI analysis will be presented.

2.1.1 Brain stem imaging

Pulsatility of blood flow in the brainstem and respiration-induced magnetic field changes can cause appreciable modulation of the signal resulting from blood oxygenation level dependence (BOLD) contrast and degrade the statistical significance of activation signals (Glover & Lee, 1995; Noll & Schneider, 1994). Many methods have been suggested to correct this noise in fMRI time series such as a method operating in the k-space domain (Hu, Le, Parrish, & Erhard, 1995) or based on image space domain called RETROCOIR. The latter might arguably overcome certain limitations of the former since it does not preclude high spatial frequency correction. In the RETROCOIR method low-order Fourier series are fit to the image data based on the time of each image acquisition relative to the phase of the cardiac and respiratory cycles, acquired using a photoplethysmograph and pneumatic belt, respectively. This method was shown to provide substantial reduction of additive noise components that arise from cardiac and respiratory functions and to perform well for both respiration- and cardiac-induced noise (Glover, Li & Ress, 2000).

Functional imaging of the brain stem is particularly susceptible to multiple kinds of physiological artefact, including quasi-periodic BOLD oscillations introduced by cardiac rhythms and respiration (Harvey et al., 2008). Brainstem imaging is controversial because it's small size and its proximity to tissues producing magnetic susceptibility effects leading to image distortion, thus, there is greater degree of noise observed in the blood oxygenation level-dependent MRI signal. Harvey and colleagues found that not only the contributions of the cardiac and respiratory signals were a source

of physiological noise but also the interaction between them so they implemented a modified version of RETROCOIR method and demonstrated that this approach improved detection of brainstem activation and might thus be usefully applied to any study examining this brain region (Harvey et al., 2008).

These methods were shown to effectively overcome to some degree cardiac and respiratory sources of noise problems, however it is not always possible to measure cardiac and respiratory signals and certain other post-hoc noise filtering or image processing methods can be applied in the analysis of the data. As an example of the latter, to increase the robustness of spatial localization of brainstem responses, a spatially unbiased infra-tentorial template (SUIT) (Diedrichsen et al., 2011) for nonlinear normalization of cerebellum and brainstem can be used. This method provides a more accurate intersubject-alignment of the brainstem than whole-brain methods. This template is based on the average anatomy of 20 young, healthy individuals, aged from 22 to 45, that preserves the anatomical detail of the brainstem to a much higher degree than the MNI whole-brain template, and improves overlap of a) deep nuclei not normally visible in T1 weighted imaging, and b) the primary fissure and the intra-biventer fissure reducing the spatial variance by approximately one third.

2.2 Ascribing cognitive function with pupillary responses

Hoeks et al (1993), proposed a model that relates pupillary variation to attentional input, physiological and psychological factors including nonvisual stimulation, habituation, fatigue and level of mental effort. They showed the pupil to be a linear time-invariant (LTI) system (Figure 7) since the effects of input pulses on the pupillary response were additive and the same attentional input pulse always generated the same pupillary response regardless of presentation time. This LTI feature of the system enabled the use of a deconvolution method to establish the impulse response function of the pupil to the input modelled as a sequence of attentional pulses – i.e. auditory or visual stimuli that can vary in number, in temporal distribution, and in pulse amplitudes- given the pupillary outputs as the continuously varying deviation of the pupil's diameter from the baseline value. The equation that governs a linear invariant system may be expressed in terms of the output of the system $y(t)$ as the convolution of the input $x(t)$ with the impulse response $h(t)$ [1]:

$$y(t) = x(t) * h(t) \quad [1]$$

Thus given an output and an input it is possible to extract the impulse response function by way of deconvolution [2]. The impulse response function (IRF) thus characterizes the behaviour of the system under the assumptions of linearity and time-invariance:

$$h(t) = \text{deconv}(y(t), x(t)) \quad [2]$$

Figure 7. Schematic of the pupil as a Linear Invariant System which impulse response $h(t)$ can be estimated via deconvolution method given the input and output signals of the system.

Hoeks and colleagues suggested a model in which the pupil response may be parameterized by a cascade model with a pre-specified number of layers representing the complexity of the pupil response in a sequence of more elementary neurobiological processes. These assume each impulse response of each layer is a decaying exponential function so, assuming each layer impulse response is the same except for an amplification factor, the impulse response of the whole system should follow an Erlang Gamma function with two feature parameters, n , where $n + 1$ represents the number of layers and t_{max} which represents the maximum of the function [3].

$$h(t) = \begin{cases} t^n e^{-nt/t_{max}}; & t > 0 \\ 0; & t \leq 0 \end{cases} \quad [3]$$

They finally use a nonlinear least squares estimation procedure to obtain the parameters n and t_{max} based on empirical data measuring pupillary responses with auditory and visual stimuli. They finally determine these parameters to be $n = 10.1$ and $t_{max} = 930 \text{ ms}$.

In Chapter 3, cognitive function using pupillary responses with visual stimuli presentation will be estimated. Since visual stimuli is used, it is necessary to dissociate the nature of pupil variations and determine whether these variations are due to cognitive processes or are light-evoked pupil constrictions responding to light fluctuations provoked by the appearance of visual stimuli. This Hoeks study suggests the use of the Erlang Gamma function with the parameters provided ($n = 10.1$; $t_{max} = 930 \text{ ms}$) to fit the cognitive aspect of the observed pupil dilation. For the visual aspect of the pupil response and assuming the pupil to be a linear invariant system with an impulse response of an Erlang gamma described in (Hoeks & Levelt, 1993), one can estimate n and t_{max} parameters for the visual aspect of the pupil responses by means of fitting pupillary canonical responses with the impulse response function. Using this framework to first fix these coefficients it is next possible to perform a General Linear Model (GLM) analysis as implemented previously (de Berker et al., 2016) to estimate the per-condition amplitude components. Given the time series of the pupil responses along the experiment and constructing every column of the design matrix from the

convolution of the corresponding gamma function (visual or cognitive) with the onset of the stimuli for every condition, it is possible to estimate the beta parameters (amplitudes) for each condition and pupil response nature (cognitive or visual) (Figure 8).

Figure 8. Scheme of the calculation of the design matrix for the GLM analysis to extract the parameter estimates for each condition of the experiments for both aspects of the pupillary responses. Each column of the design matrix is calculated by the convolution of each experimental condition onsets and the Erlang gamma response corresponding to either the cognitive or the visual aspect of the pupillary response.

2.2.1 Pupil Diameter as an indirect index of LC activity

In this thesis, pupillary responses are used as an indirect index of LC activation. Pupil diameter has been shown to be a reliable, indirect index of LC activation, positively correlating with LC firing rates in non-human primates (Gilzenrat, Cohen, Rajkowski, & Aston-Jones, 2003; Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010; Jepma & Nieuwenhuis, 2011; Joshi, Li, Kalwani, & Gold, 2016; Rajkowski, Kubiak & Aston-

Jones, 1993; Varazzani et al., 2015) and with BOLD activity in human LC (Alnaes et al., 2014; Murphy et al., 2011a).

Evoked pupil dilation has been proposed to reflect the LC phasic response in non-human primate during a target detection task (Figure 9) (Gilzenrat, Cohen, Rajkowski & Aston-Jones, 2003; Gilzenrat et al., 2010).

Figure 9. Figure modified from (Gilzenrat, Cohen, Rajkowski & Aston-Jones, 1993) showing the close relationship between tonic pupil diameter and baseline firing rate of a LC neuron while the monkey was performing fixation of visual spot during target detection task.

A recent study in monkeys (Joshi et al., 2016) suggested that non-luminance-mediated changes in pupil diameter might reflect LC activation. During a fixation task they showed a positive correlation between average pupil diameter and average spike rate over several seconds in LC. They also showed certain patterns on both spike triggered changes in pupil diameter and in pupil-triggered spike rates. For the former they showed a brief earlier dilation and a later constriction and for the latter a peak positive modulation occurred, on average, in a relatively restricted time frame just prior to the pupil event. Additionally, they observed a more strongly negative LFP value preceding dilations compared with constrictions. In general they found that LC activity was higher just preceding pupil dilations compared with constrictions, implying that the pupil changes do not cause changes in LC activation, rather they reflect underlying changes in arousal. It was also demonstrated how external events that can cause changes in arousal, such as a brief loud startling tone during randomly chosen trials, caused a transient dilation of the pupil. Another important finding from this study was the observation that manipulation of neuronal activity on the LC via microstimulation evokes transient increases in pupil diameter within 1 s of microstimulation onset.

In summary, it is possible to conclude that the activity of LC neurons are related to subsequent changes in pupil diameter during stable, near fixation under several conditions: (1) trial-by-trial associations between average pupil diameter and concurrent, tonic LC activation; (2) changes in spiking and LFP activity that occur just prior to pupil dilations; (3) trial-by-trial associations between the magnitude of pupil and LC neural responses evoked by unexpected presentations of the same auditory

stimulus; and (4) evoked changes in pupil diameter via electrical microstimulation in the LC.

The first study in humans that detailed the interrelationship between performance dynamics on a widely used attentional task and pupil diameter as an indirect index of LC-NE system activity was performed by (Murphy et al., 2011). In a new set of experiments, the same authors have recently demonstrated a positive correlation between continuous pupil diameter and BOLD activity in a dorsal pontine cluster overlapping with the LC by simultaneously recording pupilometry and fMRI both at rest and during performance of a two- stimulus oddball task (Murphy, O’Connell, O’Sullivan, Robertson, & Balsters, 2014). LC was localized via both neuromelanin-sensitive structural imaging (Shibata et al., 2006) and a previously published LC atlas (Keren, Lozar, Harris, Morgan, & Eckert, 2009). This relationship was present with and without spatial smoothing of the fMRI data, and survived retrospective image correction for physiological noise (Glover, Li & Ress, 2000). This study was the first demonstration in human of a fundamental characteristic of LC activity previously found in monkeys: phasic modulation by oddball stimulus relevance (Aston-Jones, Rajkowski, Kubiak & Alexinsky, 1994; Rajkowski, Kubiak, & Aston-Jones, 1994; Rajkowski, Majczynski, Clayton, & Aston-Jones, 2004).

Together, these findings highlight the potential for utilizing pupil diameter to better address the LC–NA system in human cognition given the lack of reliable non-invasive measures of LC activity. Thus, in experimental designs where the two types of

measurements are not made simultaneously, this study lends support to the use of pupil diameter as an indirect index of human LC activity.

2.3 Intracranial recordings

Electrical activity of single cells or cell assemblies can be measured by means of surgically implanted deep electrodes. For ethical reasons these kinds of measures have relied mostly on animal research due to the invasive nature of the technique. For this reason the most commonly used technique in humans are limited to hemodynamic techniques, such as functional magnetic resonance imaging (fMRI) or magneto-electrical techniques recorded at the scalp, including such techniques as electroencephalography (EEG) or magnetoencephalography (MEG).

However, certain invasive brain recordings can be performed in patients during various clinical procedures that can be divided into two types of categories: intraoperative and chronic or semi chronic conditions involving the implantation of deep electrodes for diagnosis or treatment. Intraoperative recordings can be performed on awake patients in the surgery room due to the lack of pain receptors in the brain and can facilitate functional mapping of the brain by electrical stimulation (Penfield, 1954). This surgery is performed mostly either by pharmacologically resistant epileptic patients in order to identify epileptic foci and posterior resection, in brain tumours cases to preserve critical brain functions (Ojemann, 2010), or to patients that undergo Deep Brain Stimulation procedures (DBS) in which chronic stimulation is used to ameliorate disabling symptoms in several neurological or psychiatric disorders such as Parkinson's disease, essential tremor, dystonia, Obsessive Compulsive Disorder (OCD), schizophrenia, and major depression among others. After the surgery, for a limited period of time, these kinds of patients have these electrodes externalized. In the case of epileptic patients,

during this period they are monitored and stimulated to localize the epileptic foci or, as in case of DBS patients until they have their pulse generator inserted. This externalization of the electrodes can be used to record intracranial EEG (iEEG).

During (iEEG) recordings, electrical signals that can be recorded from a large population of cells, the Local Field Potentials (LFP), near the electrode tip. LFPs are defined as extracellular voltage changes resulting from both dendritic currents and action potentials of populations of neurons and the signal recorded is most probably reflecting activity corresponding to input to the cells, although they could also, to some degree, contain a measure of membrane potentials and changes relating to intrinsic cellular properties (see Buzsáki, 2002; Logothetis & Wandell, 2004 for review). These signals are widely studied in both time and frequency domains to explore temporal and spectral differences in activation of population cells under different behavioural conditions within a task. In the temporal domain, Event Related Potentials (ERPs) represent the average signal across trials of the recorded LFP signal locked to some event of interest (e.g. onset of the stimuli or response time). In the frequency domain power for different frequency ranges and times can be both assessed and estimated using time-frequency analysis (Mukamel & Fried, 2012). A wide range of other interesting types of analyses can be done using the LFP signals to further explore the relationship between amplitude and phase of different frequency bands with higher frequencies seen as representing the single unit firing and lower frequencies modulating them. These analyses are known as Cross Frequency Coupling (see section 2.3.1 for more detail).

These signals are typically recorded invasively using macro-electrodes. These types of electrodes provide ~1–2 mm spatial resolution and a temporal resolution of milliseconds with higher signal to noise ratio than other techniques such as EEG or MEG. Additionally, the spatial density of electrodes can provide relatively large coverage of the brain depending on the intervention type. By contrast micro-electrodes (or microwires) can record from individual neurons (single units). The data presented in this thesis only pertain to macro-recording.

However there are limitations to this technique. It is obvious that these recordings are only conducted in patients so even if the data is properly pre-processed and artifactual activity is rejected (e.g. epileptic spikes) or recorded from non-pathologic regions; it can be argued that results cannot be generalized to a healthy population. Depth electrode implantation is not targeting the whole brain, instead a small subset of electrodes are implanted in regions of interest that depend on the clinical procedure. Another important limitation of this procedure relates to the fact that patients are normally under medication which likely complicates interpretation of the recorded neuronal signal. Another potential constraint for these recordings is the time taken for clinical setup and that monitoring of the state of the patient can limit effective task-times to between 15 and 40 minutes. In general, the heterogeneity of these subjects as compared to samples of healthy control volunteers may also confound the likelihood of obtaining reliable comparative estimates.

However, notwithstanding these points, LFP recordings represent a unique opportunity to explore otherwise hidden, but rich and complex, aspects of human cognition such as episodic memory or novelty.

2.3.1 Cross-Frequency Coupling measures accounting for Gamma and Theta code

Several signal processing tools have been developed to quantify theta-gamma coupling (more generally termed cross-frequency coupling or CFC) (Canolty et al., 2006; Cohen, 2008; Hayes, Nadel, & Ryan, 2007; Kramer, Tort, & Kopell, 2008; Onslow, Bogacz, & Jones, 2011; Penny, Duzel, Miller, & Ojemann, 2008; Tort, Komorowski, Eichenbaum, & Kopell, 2010; Young & Eggermont, 2009). Thus, high values of coupling indicate that gamma amplitude is a function of theta phase. These examples all use cross frequency coupling methods for estimating gamma amplitude modulated by theta phases.

In this section I will discuss different ways for estimating coupling between different frequency ranges in a signal. In general, in different methods for calculating cross frequency coupling it is first necessary to decompose the signal into its phase and amplitude components. This is possible using the Hilbert transform defined in [4]:

$$y[n] = H(x[n]) = h[n] * x[n] = \frac{1}{\pi} \int_{-\infty}^{\infty} \frac{x[\tau]}{n - \tau} d\tau \quad [4]$$

Where $y[n]$ is the Hilbert transform, H of the signal $x[n]$ and n is the discrete-time index. From the duality properties of the Fourier transform, convolution in the time domain with the band-limited impulse response function $h[n] = 1/\Pi$ after taking Fourier transforms, represents a multiplication in the frequency domain [5]. As long as the sampling rate satisfies the minimum Nyquist criteria, perfect recovery of the original sampled signal will be possible, and aliasing avoided.

$$H(w) = h(w) x(w) = \begin{cases} -j; w > 0 \\ j; w < 0 \end{cases} = -j \text{sign}(w); \quad [5]$$

Cross frequency coupling methods normally explore different frequency bands so the band pass filtered signal in the Theta (θ) and Gamma (Y) bands can be denoted as follows $x_\theta[n]$ and $x_Y[n]$ before applying the Hilbert transform. An analytic representation of the complex signal can be expressed by the sum of the real part, which is the original signal, and the imaginary part which is derived from the Hilbert transform [6]:

$$z_\theta[n] = x_\theta[n] + j \cdot y_\theta[n]; \quad [6]$$

Which can be also be expressed in terms of the modulus $A_\theta[n]$ and phase $\varphi_\theta[n]$ shown in [7]:

$$z_\theta[n] = A_\theta[n]e^{j\varphi_\theta[n]} \quad [7]$$

This amplitude and phase of the band pass filtered signal can be calculated as follows [8][9]:

$$\varphi_\theta[n] = \tan^{-1} \frac{y_\theta[n]}{x_\theta[n]} \quad [8]$$

$$A_\theta[n] = |x_\theta[n] + y_\theta[n]j| = \sqrt{x_\theta[n]^2 + y_\theta[n]^2} \quad [9]$$

Where $A_\theta[n]$ is the envelope of the signal, denoted subsequently as $v_{x_\theta}[n]$, and $\varphi_\theta[n]$ is the instantaneous phase.

Normally, exploring correlations between different features of the signal (amplitude, phase, and envelope) can establish cross frequency coupling measures. The formula for the correlation, ranging from -1 to 1, between different signals is given by [10]:

$$\text{Corr}(y[n], x[n]) = \frac{\sum_{n=1}^N (y[n] - \bar{y})(x[n] - \bar{x})}{N\sigma_y\sigma_x} \quad [10]$$

Figure 10. Different types of cross frequency coupling interactions taken from (Jensen & Colgin, 2007)

Figure 10 illustrates the possible ways in which different frequency bands can interact with one another to produce different types of coupling. The following subsections will provide a brief overview of every type of CFC.

2.3.1.1 Amplitude to amplitude CFC

Figure 10 (a) shows an example of a theta signal with fairly constant frequency of for example 8 Hz whose amplitude varies across time in red. In (b) is an example of a power to power coupling. In (b) it is clear how changes in the gamma frequency

amplitudes relate to power changes in the lower frequencies can be elicited. One way of accounting for this coupling between envelopes could be exploring the time resolved cross-correlation between the envelopes of both signals [11] (Bruns & Eckhorn, 2004).

$$CFC - AA = Corr(v_{x_\theta}[n], v_{x_Y}[n]) \quad [11]$$

For this purpose it would be also equivalent to use the “Coherence value” between envelopes in the frequency domain.

$$S_{v_{x_\theta}v_{x_Y}}(f) = \langle V_{x_\theta}(f)V_{x_Y}^*(f) \rangle \quad [12]$$

$$C_{v_{x_\theta}v_{x_Y}}(f) = \frac{S_{v_{x_\theta}v_{x_Y}}(f)}{\sqrt{S_{v_{x_\theta}v_{x_\theta}}(f)S_{v_{x_Y}v_{x_Y}}(f)}} \quad [13]$$

$$Coh_{v_{x_\theta}v_{x_Y}}(f) = |C_{v_{x_\theta}v_{x_Y}}(f)| \quad [14]$$

Where $S_{v_{x_\theta}v_{x_Y}}(f)$ [12] is defined as the cross spectrum of the two envelopes, $V_{x_\theta}(f)$ is the complex Fourier transform of the time series, $*$ represent the conjugate, $\langle \rangle$ represent means expectation value, $C_{v_{x_\theta}v_{x_Y}}(f)$ [13] is defined as Coherency measure and $Coh_{v_{x_\theta}v_{x_Y}}(f)$ [14] is defined as coherence as defined in (Nolte et al., 2004). Statistical significance can be estimated by temporal shuffling of the signals relative to

each other as performed in (Bruns & Eckhorn, 2004). This shuffling can be performed by repeating the computations on shuffled data sets with the average temporal structure of the signals preserved. Shuffled data can be performed in several ways. It consists of generating a dataset preserving autocorrelation values of the signal – e.g., for each trial generate a random draw at equal probability envelope in the theta band- then repeated the shuffling for N randomizations in a bootstrap procedure resulting in a shuffled distribution and cumulatively estimate a distribution for the coupling value in question. Then the significance value can be obtained by estimating the deviation of the true coupling value from this distribution.

2.3.1.2 Phase to phase CFC

In Figure 10 (c) an example of phase to phase CFC is shown, meaning the k:m phase-locking occurs between oscillations at different frequencies. In each slow cycle, there are four faster cycles and their phase relationship remains fixed. Here it is possible to observe phase velocity (the rate at which the phase of the signal varies along time) of the higher frequencies should be an integer number ($m = 4$) times the phase velocity of the lower frequencies. Thus, the phases of the 8 Hz and the $4 \times 8 = 32$ Hz oscillations are locked. This can be estimated using bispectra (Schack, Vath, Petsche, Geissler, & Möller, 2002) and wavelet techniques (Belluscio et al., 2012).

This Phase–phase CFC values can be measured by the calculation of phase locking between theta and gamma oscillations determined from the instantaneous phase series of the filtered theta and gamma bands ($\varphi_\theta[n], \varphi_\gamma[n]$). This synchronization between these two phase time series can be calculated using the phase coherence measure:

Synchronization index (SI) [15]. This is a complex number whose modulus can reflect the extent to which phases are synchronized (its value can range between 0 and 1) [16] and the phase angle of the SI represents the preferred angle which is the phase of the lower frequency at which the coupling is maximal [17]. Statistical significance again is estimated by temporal shuffling of the phase of each signal relative to each other (Belluscio et al., 2012; Lachaux, Rodriguez, Martinerie, & Varela, 1999). In order to preserve the autocorrelation among segments during the randomization for the phase signals, ‘circular shifts’ can be applied to generate the shuffled distribution (Canolty et al., 2006).

$$SI = \frac{1}{N} \sum_{n=1}^N e^{j(\varphi_{\theta}[n] - \varphi_Y[n])} \quad [15]$$

$$SI_m = |SI| \quad [16]$$

$$SI_p = \tan^{-1}\left(\frac{\text{img}(SI)}{\text{real}(SI)}\right) \quad [17]$$

Where N is the number of time points, $| \cdot |$ is the modulus, *img* the imaginary part and *real* the real part. The “mean resultant length” of the distribution of the difference between phases can be therefore calculated for different k:m ratios introducing [18] in [15]. When a distribution of k:m combination deviates from a uniform distribution , with $r=0$ for uniform and $r=1$ for a perfect [15] unimodal distribution. The Rayleigh test

is used to assess deviance from uniformity, e.g., it means that the phase difference ($\Delta\varphi_{k:m}$) oscillates around some constant value.

$$\Delta\varphi_{k:m} = k \varphi_{\theta}[n] - m\varphi_Y[n] \quad [18]$$

For calculating phase-phase coupling other methods can be used. The investigation of spectral functions of third order can be used –e.g., cross-bispectrum, cross-biamplitude and cross-bicoherence- in order to detect non-linear phase coupling between rhythms of possibly different frequencies. For more details about this methods see (e.g., Schack et al., 2002; Tass, Rosenblum, Weule, Kurths, & Pikovsky, 1998).

However, this measures of phase to phase coupling must be carefully investigated, they should rely on appropriate statistical controls –e.g., by bootstrapping- and pay particular attention to the presence of potential confounding factors. There is a recent study using simulated data and LFPs from the rat hippocampus, showing that the quasi-linear phase shifts introduced by filtering lead to spurious coupling levels, which are highly dependent on epoch length. Thus apparently significant coupling may be falsely detected when employing improper surrogate methods for statistical analysis. They also showed that waveform asymmetry and frequency harmonics may generate artifactual n:m phase-locking (Scheffer-Teixeira & Tort, 2016).

2.3.1.3 Phase to amplitude

In this type of CFC the phase of the lower frequencies modulates the amplitudes of higher frequencies. This can be calculated using different approaches as has been suggested in previous literature (Cohen, 2008; Tort et al., 2010). A common approach to analyse phase–amplitude cross-frequency coupling would be to first extract the spectral component of interest. As explained before this step would imply band-pass filtering and extraction of phase and amplitude for the relevant frequency bands. Then correlation between components (phase and amplitude) should be assessed, for example by performing the same uniformity statistical tests as used in phase-phase coupling except in this case the aim is to assess uniformity of the histogram of mean amplitude versus the phase. Then in a final step statistical outcome evaluation is needed. Parametric or non-parametric approaches comparing to suitable surrogate data can be used to assign a P-value to the observed coupling strength (Aru et al., 2015).

This can be estimated with the synchronization between two time series of phases. The phase of the gamma envelope ($\varphi_{v_{x_Y}}[n]$) and the phase of theta ($\varphi_{\theta}[n]$), can be calculated using the phase coherence measure introduced before as Synchronization index (SI) [15] in a given time window. Repeating these steps for different time frequency windows a full map of cross-frequency coupling in time-frequency space can be generated (Cohen, 2008).

Others have described similar methods for estimating phase-amplitude CFC measure. In (Tort et al., 2010) they use a Modulator Index (MI) calculated as follows. They construct the composite time series with the envelope of the higher frequencies ($v_{x_Y}[n]$)

and the phase of the lower ($\varphi_\theta[n]$), which gives the amplitude of the envelope of gamma at each phase of theta. They calculate first the average of the envelope signal at different phase bins and normalize it by dividing each bin value by the sum over the bins to obtain the normalized P as a discrete probability density function [19]. Then the MI is obtained by measuring the divergence of the observed amplitude distribution from the uniform distribution.

$$P(i) = \frac{\langle v_{x_Y}[n] \rangle(i)}{\sum_{k=1}^N \langle v_{x_Y}[n] \rangle(k)} \quad [19]$$

Where i is each phase bin and N is the total number of phase bins.

More detail on other methods of calculating this CFC measure can be found in (Canolty et al., 2006; Cohen, 2008; Colgin et al., 2009; Jiang, Bahramisharif, van Gerven, & Jensen, 2015; Lakatos, Shah, Knuth, & Ulbert, 2005; Penny et al., 2008). As reviewed in (Tort et al., 2010) all represent advantages and disadvantages of the two methods described.

Despite the general belief that PAC measures are an essential tool for understanding temporal organization of hierarchical neural computations, some debate was raised after a demonstration that signals with abrupt changes can leads to spurious CFC measures (Kramer et al., 2008), also taking an example of a Van der Pol Oscillation (nonlinear relaxation oscillator) a CFC analysis would lead to the conclusion of lower phases modulating higher frequencies and these spectral correlations are due to the

nonlinearities of the single oscillator (Aru et al., 2015). Furthermore nonstationary processes, such as most neural signals in general, would exhibit spectral correlations missed by a stationary Fourier expansion that could be misinterpreted (Lii & Rosenblatt, 2002). Also recent studies (Cole et al., 2016; Sheremet, Burke, & Maurer, 2016) provided concrete examples of human and rat hippocampal recordings with non-sinusoidal oscillations contributing to PAC estimates. Lower frequency periodic but non sinusoidal signals can be expressed, by their Fourier decompositions, as a weighted sum of harmonics. The more the periodic signal deviates from a sinusoid the larger the number of harmonics required to represent it. As illustrated in (Jensen, Spaak, & Park, 2016) measures of PAC are sensitive to higher harmonics not reflecting neural activity. The problem of estimating apparently high-frequency but spurious harmonics, from low frequency non sinusoidal signals, using PAC measures can be mitigated by the use of information from complementary modalities (e.g. spike field data). It is also useful when interpreting PAC results, to note that spurious estimations are not such a problem when the coupling is between different areas or layers or when it is possible to relate modulations in low frequency power to modulations in PAC (for more information see (Jensen et al., 2016)).

2.3.1.4 Envelope method: Frequency of the lower rhythms modulating the envelop of the higher

The envelope method is a time-frequency representation of the power signal (envelope) of a high frequency signal. For calculating the power signal as a function of time, data it is first segmented and multiplied by a tapered Hanning window h , M samples long with

a known spectral leakage pattern. Then a discrete Fourier transform is applied to successive windowed data segments of the signal (length M). The length of the sliding time window can be chosen to adapt in inverse proportion to increasing frequency (as in the case of Morlet wavelets), about w cycles long with respect to the frequency Y , i.e. $M = w \cdot Fs/Y$; where Fs is the sampling rate (Jiang et al., 2015). This is also known as the “*convolution method*” because it can be expressed in terms of a sliding differentiable kernel with which weighted inner products may be computed at each time index [20]:

$$v_{x_Y}[n] = \frac{1}{Fs} \left| \sum_{m=1}^M h[m] x_Y[n + m - M/2] e^{-j \frac{2\pi Y m}{Fs}} \right| \quad [20]$$

Next, a Time Frequency analysis is performed with the resulting signal using a Hanning taper assuming that only the lower frequencies are of interest.

This method was illustrated with simulated data of particular cases of modulations in which with theta and gamma signals are mixed. Phase-amplitude CFC described in (Jiang et al., 2015), was calculated as coherence between the power envelope of the high frequency band and the original signal across smoothly weighted segments. The results of Simulation 1 are illustrated in the upper row of Figure 11 and results for Simulation 2 in the bottom row. In Simulation 1 signal 1 was generated by multiplying signals with different frequencies $\theta = 10$ Hz and $Y = 83$ Hz, adding the gamma signal, the theta signal and random noise using 100 trials [21]. In simulation 2, signal 2 was

generated by mixing the signals in both bands gamma and theta and only adding gamma and random noise but not theta using 100 trials. This is known as Amplitude Modulation (AM) where the carrier signal in this case is the gamma signal and the modulation signal theta [22].

$$\text{signal1} = (\sin(2\pi\theta t) + 1) \sin(2\pi\gamma t) + \sin(2\pi\theta t) + \text{Gaussian noise}(0,1) \quad [21]$$

$$\text{signal2} = (\sin(2\pi\theta t) + 1) \sin(2\pi\gamma t) + \text{Gaussian noise}(0,1) \quad [22]$$

In Figure 11 it is shown how when theta is added in the signal, using phase-amplitude CFC method it is possible to observe how the phase of theta is modulating the amplitude of gamma—first simulation, upper row-, while when the theta component is not present -the second simulation, bottom row- it is not possible to identify the modulation (notice the different scale of the coherence values for the PAC in both simulations). Conversely the time frequency representation of the envelope of the gamma signal shows for both modulations that the envelope is being modulated by the lower frequencies.

Figure 11. Simulation comparing PAC measure and envelope method. Columns show the raw signal, power spectrum analysis and analysis for both methods of CFC. Upper row shows the results for the first simulation using signal 1 and bottom row for the second using signal 2.

The CFC envelope method may also be used for assessing how the power spectrum of the envelope of the high frequency activity that could represent single unit spiking may be modulated by lower frequency signals. Notice that this method is especially useful in cases where, for example, there is observable Theta power that can be suppressed at certain time periods.

Note that the occurrence of different CFC are not mutually exclusive, it might be the case that, for example, the theta phase modulates both frequency and power of the gamma

Chapter 3

Taking action boosts episodic memory encoding in humans via engagement of noradrenergic system

3.1 Abstract

We are constantly interacting with our environment at the same time as we encode memories. However, how actions modulate memory formation remains poorly understood. Goal-directed movement engages the locus coeruleus (LC), the main source of noradrenaline (NE) in the brain. NE is known to enhance episodic encoding, suggesting that action could improve episodic memory via LC engagement. Here we demonstrate, across seven experiments, that episodic memory encoding is enhanced by action (Go responses), compared to action inhibition (NoGo). In support of a noradrenergic mechanism underlying this enhancement, functional magnetic resonance imaging, and pupil diameter as a proxy measure, show enhanced memory encoding-related LC activity during action. A final experiment confirmed a novel prediction that emotionally aversive stimuli, which recruit the NE system, modulate the mnemonic advantage conferred by Go responses relative to neutral stimuli. We therefore provide converging evidence that taking action boosts episodic memory encoding via a noradrenergic mechanism.

3.2 Introduction

Much of the episodic memories we form in daily life are encoded whilst we are physically interacting with the environment. However, the extent to which actions influence episodic memory encoding is currently unknown. Research on educational techniques shows that “active learning”, an instructional method that stimulates student activity in class, such as making button-press responses, is more effective than passively receiving information from an instructor (Martyn, 2007; Prince, 2004; Rieber, 1996). However, within this framework, students typically make motor responses to questions posed by the instructor, thus the effect of the action *per se* (button-press alone) on learning cannot be identified. This raises the question whether taking action influences the formation of memory.

3.2.1 Action, learning and memory literature

In laboratory tests of memory, encoding tasks frequently involve a voluntary movement (typically a button press), but it has been the effect of the cognitive process leading to the movement -e.g., deep and shallow encoding tasks- (Craik & Lockhart, 1972) that has been the focus of memory research, as opposed to isolating the effect of the movement on memory encoding. A link between voluntary movement and episodic memory has been studied on the enactment effect, which describes an improvement of subsequent retrieval for action phrases (e.g., “pick up the book”) when participants perform the actions during encoding compared with merely listening to or reading the phrases (Engelkamp & Cohen, 1991; Engelkamp, Zimmer & Biegelmann, 1993; Zimmer, 2001). Yet, since the memory tested in this task is related to the movement, it

remains unknown whether the memory of the movement can be dissociated from the effect of engaging the motor system on memory. An example of the latter effect would be a difference in the likelihood of remembering the title of a book if we are cued to pick it up relative to if we simply look at the same book on the library shelf.

In contrast, there is also recent evidence showing inhibition response-induced episodic memory impairment suggesting that there should be a higher inhibitory resource demand during encoding of subsequent forgotten stimuli compared to remembered leading to memory encoding regions having less resources available during encoding (Chiu & Egner, 2014, 2015).

3.2.2 Neural mechanisms

A possible relationship between action and episodic memory is suggested by action-related neuronal responses in two brain areas: the medial temporal lobe (MTL) and the locus coeruleus (LC). MTL structures, particularly hippocampus, are critical for episodic memory and spatial navigation (O'Keefe & Nadel, 1978; Scoville & Milner, 2000; Squire, 1992; Strange, Witter, Lein & Moser, 2014; Tulving, 1972). In rodents, hippocampal theta activity has been shown to increase with gross voluntary types of movement such as rearing and jumping (Vanderwolf, 1969). Furthermore, the activity of hippocampal place cells, which fire when the animal visits a specific area in a familiar environment (O'Keefe, & Nadel, 1978), is also strongly dependent on movement-related information (Chen, King, Burgess, & O'Keefe 2013). In humans, intracranial recordings from the medial temporal lobe reveal that voluntary movements of the arm or tongue, in contexts not requiring explicit memory encoding, modulate

neuronal firing rates in hippocampus (Halgren, 1991) and surrounding cortex including parahippocampal gyrus (Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010).

There is also evidence in humans showing that motivation enhances episodic memory formation by taking action through interactions between medial-temporal lobe (MTL) structures and dopaminergic midbrain suggesting an episodic memory enhancement for events that are worth acting for (Koster, Guitart-Masip, Dolan, & Düzel, 2015). This raises the question if reward expectation is necessary to influence episodic memory through action.

The LC is the main source of noradrenaline (NE) in the brain, neuromodulator known as well to modulate episodic memory (Cahill et al., 1994; LaBar & Cabeza, 2006; McGaugh, 2000, 2004; Segal & Cahill, 2009; Strange & Dolan, 2004; Strange et al., 2003; Tully et al., 2010). Recent single-unit recordings of the LC in non-human primates demonstrate increased activity before the onset of the movement or with the onset of the stimuli presentation led to the suggestion that LC phasic response is driven by the outcome of a decision process and the commitment to act (Bouret, & Richmond, 2009; Bouret & Richmond, 2015; Clayton et al., 2004; Kalwani et al., 2014; Pavlenko & Kulichenko, 2003; Varazzani et al., 2015). It could be possible that later components of the LC activation would produce NE liberation after motor circuits are already activated. This implies that the LC response triggered by an action may serve functions in addition to facilitate the behavioral response such as memory function.

3.2.3 Objective, Methods, Hypotheses/Prediction

In summary, there is evidence showing that taking action engages LC activity, which is the main source of noradrenaline in the brain – neuromodulator well known to enhance episodic memory. In addition, taking action also engages memory related areas such as hippocampus and parahippocampal gyrus. Together with evidence showing that enactment enhances episodic memory raise the hypothesis of a possible memory modulation by voluntary movement mediated by noradrenergic mechanism. However, direct evidence of such relation between memory and unrelated voluntary movement is currently lack.

The rationale of the current study was to investigate if, and how, taking action influences episodic memory. To address how encoding of a visual stimulus is influenced by presentation in the context of simultaneous voluntary movement (“Go” button-press response) compared to withholding of movement (“NoGo” response) is examined using a Go/NoGo task.

Traditionally Go-NoGo tasks have been extensively employed to study goal-directed responding and response inhibition, in which subjects have to respond to a target stimulus (Go) and to inhibit their response to a non-target stimulus (NoGo). The majority of ERP studies have interpreted the NoGo-related N2/P3-complex as an indicator of the inhibition of a response (e.g., Falkenstein, Hoormann, & Hohnsbein, 1999; Kaiser et al., 2006). Several fMRI studies revealed contributions of subthalamic nucleus (STN), putamen, medial frontal and posterior cingulate cortices to inhibition response in the context of a Go-NoGo task (Aron, 2007; Simmonds, Pekar, &

Mostofsky, 2008). Interestingly, a pupillometry study found that dilation was influenced by the requirement of a button press in the context of a target detection task (Privitera, Renninger, Carney, Klein, & Aguilar, 2010).

At the same time ERPs and other neuroimaging techniques such as fMRI have been widely used to study episodic memory encoding in long-term memory tasks, often using the subsequent-memory paradigm (e.g., Cansino & Trejo-Morales, 2008). In this paradigm, brain activity is recorded during a memory-encoding phase and uses it to predict subsequent success or failure during a retrieval phase. Several fMRI studies have repeatedly reported MTL activation including hippocampal and surrounding cortices such as parahippocampal gyrus to have a fundamental role in episodic memory encoding (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Kirchoff, Wagner, Maril, & Stern, 2000). Interestingly, pupillometry has been also used to study episodic memory encoding. Pupil size during scene presentation has been also shown to be modulated by recognition memory in humans (see Goldinger & Papesh, 2012 for review) and in monkeys (Montefusco-Siegmund, Leonard & Hoffman, 2016). Pupil diameter has been also shown to positively correlate with LC firing rates in non-human primates (Gilzenrat et al., 2003; Gilzenrat et al., 2010; Jepma & Nieuwenhuis, 2011; Joshi et al., 2016; Rajkowski et al., 1993; Varazzani et al., 2015) and with BOLD activity in human LC (Alnaes et al., 2014; Murphy et al., 2011a).

On the basis of these findings, we hypothesized that taking action would enhance episodic memory encoding by engaging medial temporal lobe memory circuits via recruitment of the noradrenergic system. Behavioral experiments to test our hypothesis

that voluntary movement modulates episodic memory encoding were initially performed. Subsequent experiments employing fMRI, pupillometry, manipulation of the emotional content of encoded material and reward expectation have been sequentially designed to provide converging evidence that Go-associated encoding enhancement is mediated by the adrenergic system.

3.3 Methods

3.3.1 Participants

A total of 237 human subjects (aged 18-35; 116 female) were recruited via advertisement to participate in our study. Participants were right- or left-handed for the behavioral experiments and all right-handed for the fMRI experiment, had no history of neurological or psychiatric disease, and normal or corrected-to-normal visual acuity. All participants provided written informed consent prior to commencement of the study. The study was approved by the ethical committee of the Universidad Politecnica de Madrid.

3.3.2 Psychological task

The experiment consisted of two phases: visual stimulus encoding in the context of a Go-NoGo task followed by a later surprise recognition test. For Exp 1-6, 190 grayscale photographs of objects were presented in randomized order during encoding. Participants were instructed to press a button (go trials) when the images were presented with a particular color frame (blue or yellow). The color frame for the “Go” and “NoGo” instruction were balanced across participants in all experiments. Go and No-Go frames appeared with equal probability (i.e. both at 50% probability). Participants were instructed to look at the center of the screen. Stimuli were displayed visual angle at a viewing distance of 60 cm. Participants returned after one hour for Exp1-6, and after one day in Exp 7, in order to perform a surprise recognition test. For Exp1-6, a total of 380 images – the 190 that were presented at encoding and 190 new “foils” – were

presented in randomized order with no frames on a black background (Table 1). Participants were required to indicate whether they remembered (R), were familiar with (K) or did not remember (forgotten, F) the image from the encoding phase (Figure 12). For Exp 7, participants performed a similar Go/NoGo task but with color images selected from the International Affective Picture System (IAPS) Database (Figure 13). We selected a total of 80 images, 40 neutral and 40 negative emotional, with the following arousal and valence ratings: emotional stimuli arousal score (std) 6.46 (0.49) and valence score 2.27 (0.85); neutral stimuli arousal score 2.89 (0.41) and valence score 5.00 (0.24), using a scale from 1-9 with 1 being the most negative valence and 9 most arousing. At encoding, participants were presented with 20 emotional and 20 neutral images (randomly selected from the pool of 80 images). Again, images were presented in random order with a color frame indicating the requirement of pressing a button for the Go trials or not pressing for the NoGo trials. A surprise recognition phase was conducted 24 hours after, during which all 80 images were presented in random order. Again, participants made a Remember/Familiar/New judgment for each stimulus.

For all experiments, exclusion criteria were applied on the basis of task performance at encoding and recognition. Participants performing at less than 90% correct button press for Go, and 90% correct withheld responses for NoGo, trials were excluded from analyses. Furthermore, those participants with poor memory performance (defined as correct hit remembered rate minus remember false alarm rate less than 0%) were not further considered for analysis. In addition, participants making button-press responses for less than 90% of trials during recognition testing were excluded from analyses.

3.3.2.1 Experiment 1

Image presentation time was 1s in both phases, with variable ISI from 2.3 to 3.3s at encoding and 2.8 to 3.3s at recognition. A total of 33 participants (18 women; 32 right handed; age range, 18–35 years; mean age, 26.80 years; SD, 3.20) performed the experiment. Two participants were excluded on the basis of Go/NoGo task performance.

3.3.2.2 Experiment 2

This was identical to Exp 1 except that participants were financially rewarded for responding as fast as they could, financially penalized for omission and commission errors. Participants began the experiment with a 10€ voucher and were told they could earn up to 20€ on the basis of their performance. They were informed that at the end of the experiment, 5 Go trials and 5 NoGo trials would be randomly selected and for each correct NoGo, 1€ will be added to the final quantity 0€ otherwise. For each correct Go trial they started with 1 more euro and per 0.1s of delay above 0.5s, 0.1€ were subtracted for the final amount. 29 participants (14 females; 28 right handed; age range, 18–35 years; mean age, 24.03; SD, 4.19) performed this experiment. One participant was discarded due to absent button-presses at recognition, and a further 2 participants for poor memory performance. All participants were paid 20€.

3.3.2.3 Experiment 3

In this experiment, the image presentation time was reduced from 1s to 250ms. While a colored background indicating the requirement of pressing or not pressing a button was presented for 750 ms, the images of grayscale objects were presented at 3 different onsets relative to the 0 to 750 ms color background presentation time: at 0s, at 250ms and at 500ms. The same ISI was used as in the previous experiments. Up to 52 participants performed the experiment and 38 participants (22 females; 35 right handed; age range, 18–35 years; mean age, 27.97; SD, 4.26) were included in the final analysis. Five participants were rejected for poor Go/NoGo performance, 2 participants were rejected because of multiple button presses for the Go trials, 1 did not finish the task, 2 participants misunderstood the instructions and pressed when the image appeared not when the colored frame appeared on the screen, and 4 more were excluded on the basis of poor memory performance.

3.3.2.4 Experiment 4

This was identical to Exp 1 except that stimuli were presented for 250ms. 27 participants (16 females; 26 right handed; age range, 18–35 years; mean age, 26.74; SD, 4.92) took part in this experiment. Five participants were removed from the analysis: 3 on the basis of Go/NoGo performance and 2 were excluded on the basis of low response rate during recognition.

3.3.2.5 Experiment 5

This experiment is a replication of Exp 4 but in the context of fMRI scanning. Thirty-eight participants (25 females; 38 right handed; age range, 18–35 years; mean age, 25.34; SD, 5.06) began this experiment. On the basis of stimulus-correlated head movement we excluded 6 participants at encoding phase, 1 other subject was excluded due to signal drop out in medial temporal lobe, 6 other participants were rejected because they presented less than 85% of correct Go or NoGo trials or answers at recognition phase, 1 other because multiple button press for the Go condition and 3 were removed because of poor memory performance.

3.3.2.5.1 fMRI data acquisition

For each subject, a 3T Siemens Trio TIM system was used to acquire MPRAGE T1-weighted anatomical images with 1mm³ resolution (repetition time (TR), 2300 ms; echo time (TE), 2.98 ms; flip angle, 9°). During encoding, 288 gradient-echo echo-planar T2*-weighted MRI image volumes with blood oxygenation level-dependent contrast were acquired, plus five additional volumes, acquired at the start of each session and subsequently discarded, to allow for T1 equilibration effects. Each whole-brain volume comprised 40 axial slices (2.2mm thick; distance factor 0.25; repetition time 2.43 s; echo time 30 ms; flip angle 90°) sequentially acquired (ascending).

3.3.2.5.2 fMRI data analysis

Functional imaging data were analyzed using statistical parametric mapping (SPM8; <http://www.fil.ion.ucl.ac.uk/spm>) using an event-related design. Each subject's fMRI time series was realigned, slice time corrected, normalized to MNI space and smoothed with an isotropic 3D Gaussian kernel of 6 mm full-width half-maximum. To test for effects of motor action on memory, we specified 6 effects of interest in a general linear model (GLM): the events corresponding to Go and NoGo trials, separated according to whether these images yielded a subsequent remember (R), familiar with (K) or forgotten (F) response at recognition testing. Event-specific responses were modeled by convolving a delta-function with a canonical haemodynamic response function (HRF) to create regressors of interest. Response errors were modelled separately. Six movement parameters were modeled as nuisance covariates.

Session-specific parameter estimates of the magnitude of the hemodynamic response for each stimulus type were calculated for each voxel in the brain. A contrast of parameter estimates modeling each comparison of interest (e.g., remembered *vs.* forgotten Go *vs.* NoGo images) was calculated in a voxel-wise manner to produce, for each subject, one contrast image for that particular effect. For the random effects analysis, each subject's contrast image was entered into a one-sample *t*-test across participants. We report group-level analyses pertaining to the main effects and interaction term of our response (Go, NoGo) by subsequent memory (Remembered, Forgotten) 2 by 2 factorial design.

In order to improve the spatial reliability of the observed LC response, the SUI toolbox (http://www.diedrichsenlab.org/imaging/suit_fmri.htm) was employed, as

described previously (Diedrichsen, 2006) (see Chapter 2.2). In brief, realigned, slice-time corrected functional images were coregistered to their subject-specific T1-weighted anatomical scan (with origin manually set at the anterior commissure). We then repeated the first level analysis described above. Again, a contrast image for the interaction term of response (Go, NoGo) by subsequent memory (Remembered, Forgotten) was calculated in a voxel-wise manner. Next, the cerebellum and brainstem were isolated in the anatomical image, and the ensuing image normalized to the SUI atlas template using a nonlinear deformation. This deformation was then applied to the contrast image created for the interaction term, and resliced, masking out activation from outside the cerebellum or brainstem. Finally, each participant's normalized contrast images were smoothed with a 6 mm kernel and submitted to a second level GLM across subjects.

We carried out a small-volume correction (SVC) to the P values of the ensuing maxima in LC and parahippocampal gyrus. For the latter, we used bilateral posterior parahippocampal mask from the Harvard-Oxford atlas. For LC maxima, we used a probabilistic LC atlas (Keren et al., 2009) normalized to the anatomical space defined by the SUI toolbox.

3.3.2.6 Experiment 6

This experiment was performed in the context of pupillary recordings. The behavioral task was identical to Exp 4, except for the presentation of a white fixation cross in the center of the screen for the last 500 ms of the trial to allow participants to blink. Thirty-five participants (21 females; 32 right handed; age range, 18–35 years; mean age, 27.31;

SD, 5.08) performed the experiment. Three participants were excluded from analyses due to excessive number of blinks (more than 10% of trials in any one of the conditions). Another 2 participants were excluded due to Go/NoGo performance and 2 more due to low memory performance

3.3.2.6.1 Pupil data acquisition

The diameter of the left pupil was measured using an EyeLink 1000 System (SR Research), sampled at 1000 Hz. Participants were sat in a darkened room, and asked to maintain fixation whenever possible. A chin rest was used to minimize movement. Iso-luminance was ensured for the grayscale objects and for the blue and yellow frames separately using Shine toolbox (www.mapageweb.umontreal.ca/gosselif/shine). (Willenbockel et al., 2010). Stimuli were displayed with at a viewing distance of 70 cm. An analogic card of EyeLink system was connected to an Analogic/Digital converter Cambridge Electronic Device (CED) and data acquired using Spike2 (CED) software. The data were subsequently exported in MATLAB (Mathworks, Natick, MA, USA) format and analyzed using the fieldtrip toolbox (<http://www.fieldtriptoolbox.org/>).

3.3.2.6.2 Pupil data analysis

Pupil diameter data were band pass filtered (0.05 to 4Hz) using a 3rd order Butterworth filter. Blinks were manually detected and corrected by cubic spline interpolation of samples 100 ms either side of the blink. Subsequently, visual artifact rejection was performed to remove bad interpolations. Condition-specific pupil diameter modulations were analyzed using a GLM approach as implemented previously (de Berker et al.,

2016). To dissociate pupil variations due to cognitive processes vs. light-evoked pupil constrictions evoked by the appearance of visual stimuli, we modeled these two response components separately. We assumed the pupil to be a linear temporal invariant system (LTI) with an impulse response function for pupillary dilation ($Diameter(t)$) described as an Erlang gamma function (Hoeks & Levelt, 1993) which follows this equation as a function of time t :

$$Diameter = \begin{cases} t^n e^{-nt/t_{max}}; & t > 0 \\ 0; & t \leq 0 \end{cases}$$

where n and t_{max} are parameters describing the number of layers of the system and gamma peak time, respectively. To model the cognitive pupillary response we used $n = 10.1$ and $t_{max} = 0.93s$, the parameters estimated in Hoeks & Levelt (1993). To model the light-evoked visual response, the participant-specific pupil response to encoded stimuli evoking a subsequent familiar (K) judgement at recognition (*i.e.*, those trials that were not included in the GLM analysis), were employed as canonical responses to estimate the parameters of interest n and t_{max} (using the `fmincon` function in MATLAB) for each participant separately (Figure 19B).

Event-specific responses for our effects of interest (Go and NoGo remembered and forgotten trials) were modeled by convolving a delta-function with the two Erlang gamma basis functions. Nuisance regressors included: the first and second derivatives of these regressors; Go and NoGo familiar trials (convolved with the visual and cognitive response function); fixation cross presentation (convolved with visual response function); button-press reaction time events (convolved with the cognitive

response function). The `glmfit` function in MATLAB was used to calculate parameter estimates for the observed (z-scored) pupil response. For each participant, the ensuing parameter estimates for the cognitive Erlang function were entered into a repeated measures ANOVA to test for a response (Go, NoGo) by subsequent memory (Remembered, Forgotten) interaction across participants (see Chapter 2.2).

Lastly, in order to measure the pupil constriction due to the light reflex, band-pass filtered, eye blink-corrected data were epoched into trials, baseline corrected and averaged across all trials for each participant. The maximal pupil constriction (minimum diameter) for each participant was then calculated, and entered into a Welch's *t*-test (due to different sample sizes) comparing participants who show enhanced memory for Go relative to NoGo stimuli *vs.* those who do not.

3.3.2.7 Experiment 7

Twenty-three participants (15 females; 23 right handed; age range, 18–35 years; mean age, 30.79; SD, 6.75) performed this experiment. The same presentation time and ISI as in Exp 4-6 were used for both encoding and recognition phases. One subject was excluded from further analysis on the basis of Go/NoGo performance and a further subject due to poor memory performance.

Figure 12. Behavioral task: Incidental memory encoding in the context of a Go/ NoGo task. At encoding, grayscale objects were presented with a color frame indicating requirement of a button press for the Go condition or withholding the response for NoGo. A surprise recognition test was conducted one hour later (or one day later Exp 7), during which participants were presented with objects from the encoding task intermixed with an equal number of lure items (presented without a frame) and indicated whether they remembered (R), were familiar with (K) or did not remember (F) the objects.

Exp	Presentation time	Recognition test interval	Performance financially	Context	N	Emotional
1	1s	1h	no	behavior	31	No
2	1s	1h	yes	behavior	26	No
3	250 ms	1h	no	behavior	38	No
4	250 ms	1h	no	behavior	22	No
5	250 ms	1h	no	fMRI	21	No
6	250 ms	1h	no	pupilometry	28	No
7	250 ms	1 day	no	behavior	21	Yes

Table 1. Summary of experimental parameters, design, participants and experimental context for Exp 1-7. Presentation time pertains to both encoding and recognition tasks N: Number of participants

Figure 13. Behavioural task: Incidental emotional memory encoding in the context of a Go/Nogo task. The same task as in previous experiments. At encoding, coloured images from the IAPs database were presented with a color frame indicating requirement of a button press for the Go condition or withholding the response for the NoGos. The same number of each condition was presented to avoid oddball memory effects. A surprise recognition test was conducted one day later, during which participants were presented with items from the encoding task intermixed with an equal number of lure items (presented without a frame and indicated whether they remembered (R), were familiar (K) with or did not remember (F) the items

3.4 Results and discussion

3.4.1 Taking action boosts episodic memory.

In the first experiment we tested for the effect of performing an action during encoding on subsequent memory performance. As predicted, we observed significantly better memory for remembered Go-items compared to NoGo-items ($t_{30} = 2.40$; $p = 0.02$), (Table 3). Successful encoding of Go-items was not modulated by response speed, as reaction times (RTs) for subsequently remembered and forgotten Go items did not differ (Figure 15B).

By contrast, memory performance for familiarity judgments was at chance level for both Go and NoGo stimuli (one-sample t -tests K hits minus false alarms, $ps > 0.49$) and did not differ between them ($t_{30} = 0.55$; $p = 0.60$). As this absence of a relevant memory signal was also generally the case for all subsequent experiments (Table 2, Figure 14), we focused all further analyses on remember accuracy and its modulation by motor response at encoding.

We replicated this action induced memory enhancement across 5 subsequent variants of this experiment, addressing the role of reward, stimulus presentation timing, and the neural mechanisms underlying this action induced enhancement of episodic memory (Figure 15A-B, Table 3).

Figure 14. Familiarity recognition behavioural results. Recognition memory for the K responses corrected by false alarms.

Experiment 1

t-test recognition memory K responses Go vs. NoGo (hits- false alarms) $t_{30} = 0.55$; $P = 0.59$

One-sample *t*-test Go $t_{30} = 0.69$; $P = 0.50$

One-sample *t*-test NoGo $t_{30} = 0.24$; $P = 0.82$

Experiment 2

t-test recognition memory K responses Go vs. NoGo (hits- false alarms) $t_{25} = 0.70$; $P = 0.49$

One-sample *t*-test Go $t_{25} = 0.70$; $P = 0.49$

One-sample *t*-test NoGo $t_{25} = 0.01$; $P = 0.99$

Experiment 3

t-test recognition memory K responses Go vs. NoGo (hits- false alarms) $t_{37} = 1.12$; $P = 0.27$

One-sample *t*-test Go $t_{37} = 1.64$; $P = 0.11$

One-sample *t*-test NoGo $t_{37} = 2.93$; $P = 0.006$

Experiment 4

t-test recognition memory K responses Go vs. NoGo (hits- $t_{21} = 0.76$; $P = 0.45$
false alarms)

One-sample *t*-test Go $t_{21} = 0.76$; $P = 0.10$

One-sample *t*-test NoGo $t_{21} = 0.76$; $P = 0.45$

Experiment 5

t-test recognition memory K responses Go vs. NoGo (hits- $t_{20} = 2.09$; $P = 0.05$
false alarms)

One-sample *t*-test Go $t_{20} = 1.09$; $P = 0.29$

One-sample *t*-test NoGo $t_{20} = 1.27$; $P = 0.22$

Experiment 6

t-test recognition memory K responses Go vs. NoGo (hits- $t_{27} = 0.63$; $P = 0.53$
false alarms)

One-sample *t*-test Go $t_{27} = 1.05$; $P = 0.30$

One-sample *t*-test NoGo $t_{27} = 0.41$; $P = 0.68$

Experiment 7

t-test recognition memory K responses Go vs. NoGo (hits- $t_{21} = -0.76$; $P = 0.45$
false alarms; collapsing across emotional and neutral stimuli)

One-sample *t*-test Go $t_{21} = -1.70$; $P = 0.10$

One-sample *t*-test NoGo $t_{21} = -0.76$; $P = 0.45$

Table 2. Summary table of the statistics for the K responses in each experiment.

Figure 15. Behavioral results: Exp 1-6 (A) Memory performance. Recognition memory for remembered (R) items corrected by false alarms for both Go and NoGo conditions for each experiment * ($P < 0.05$), ** ($P < 0.01$), † ($P < 0.05$ one-tailed). (B) Reaction times at encoding for remembered and forgotten Go stimuli. (C) Commission error rate on NoGo trials during encoding depending on the number of consecutive preceding Gos in black and Recognition memory (remember hits minus false alarms) for the NoGo condition depending on the number of consecutive preceding Gos in red.

	t-test Go vs. NoGo	P values	Cohen's d Go
Exp 1	$t_{30} = 2.40$	0.02	0.28
Exp 2	$t_{25} = 2.85$	0.009	0.37
Exp 3	$t_{37} = 3.28$	0.002	0.57
Exp 4	$t_{21} = 2.26$	0.03	0.51
Exp 5	$t_{20} = 1.41$	0.17	0.29
Exp 6	$t_{27} = 2.75$	0.01	0.40

Table 3. Summary of statistics results for Exp 1-6

3.4.2 Taking action enhances episodic memory, inhibiting action does not impair it.

Across experiments we found better memory for Go-items compared to NoGo-items suggesting that taking action can boost episodic memory. But as in our task memory performance is compared between two response requirements at encoding (Go vs. NoGo), alternatively the difference in memory could be explained by response inhibition having resulted in memory impairment (see Chiu & Egner, 2014, 2015). If the latter were the case, this would predict a modulation of NoGo-item memory as a function of the number of preceding Go items. With increasing consecutive Go trials, response inhibition mechanisms are more taxed, leading to increased commission errors (“Go” response when “NoGo” is cued) (Durstun, Thomas, Worden, Yang, & Casey, 2002; Thomas, Gonsalvez, & Johnstone, 2009). By extension, an inhibitory account of NoGo-evoked worsening of memory encoding would predict that memory for NoGo items would decrease with increasing preceding number of Go items. We did not observe such relationship. Although participants in Exp 1 indeed showed more commission errors as a function of the number of consecutive preceding Go trials – showing a linear increase ($F_{1,30} = 5.44$; $p = 0.03$) (Figure 15C; Table 4) – no effect of the number of preceding Go trials on NoGo-items memory was found ($F_{2,34,70.16} = 0.82$; $p = 0.49$). This lack of NoGo-item memory modulation on the basis of preceding Go trials, also observed in all subsequent experiments (Figure 15C; Table 4), argues against an inhibitory mechanism negatively affecting memory for NoGo items. We conclude

that action inhibition does not account for the differential Go vs NoGo memory performance we observe.

	Comission errors by number of preceding Go	Linear Contrast	Memory performance for the NoGo by number of preceding Go
Exp 1	$F_{1.88,56.44} = 1.9; p = 0.16$	$F_{1,30} = 5.44; p = 0.03$	$F_{2.34,70.16} = 0.819; p = 0.49$
Exp 2	$F_{1.685,42.13} = 0.867; p = 0.41$	$F_{1,25} = 1.56; p = 0.22$	$F_{2.09,52.17} = 0.36; p = 0.71$
Exp 3	$F_{2.1,77.684} = 2.496; p = 0.086$	$F_{1,37} = 4.643; p = 0.04$	$F_{1,3} = 0.373; p = 0.545$
Exp 4	$F_{1.7,35.75} = 2.965; p = 0.072$	$F_{1,21} = 7.79; p = 0.01$	$F_{2.09,43.97} = 1.40; p = 0.26$
Exp 5	$F_{1.741,34,825} = 2,337; p = 0.118$	$F_{1,20} = 3,926; p = 0.06$	$F_{2.53,20.66} = 0.059; p = 0.97$
Exp 6	$F_{1.3,34.97} = 3.55; p = 0.058$	$F_{1,27} = 4.72; p = 0.39$	$F_{1.75,47.38} = 1.42; p = 0.25$

Table 4. Commission errors depending on the preceding Gos statistics summary and memory performance for the NoGos depending on the number of consecutive preceding Gos

3.4.3 Taking action enhances episodic memory regardless of reward anticipation.

Recent data suggest that memory formation might be promoted by anticipation of reward motivation through interactions between medial temporal lobe (MTL) structures

and dopaminergic midbrain (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Koster et al., 2015; Lisman, Grace, & Duzel, 2011; Murty, LaBar, Hamilton, & Adcock, 2011; Otmakhova, Duzel, Deutch, & Lisman, 2013; Shohamy & Adcock, 2010; Wolosin, Zeithamova, & Preston, 2012). The recent evidence that button-press Go responses in anticipation of reward can improve memory encoding (Koster et al., 2015) raises a possibility that a Go response in the current task reflects an approach-related action that engages the reward system which, in turn, strengthens episodic memory. If this were the case, the ensuing prediction would be that explicit anticipation of financial reward evokes greater action-evoked memory enhancement than observed in Exp 1. Thus, the design of Exp 2 was identical to Exp 1 (frame-cue and picture presented simultaneously) except that participants were financially rewarded for responding as fast as they could, and financially penalized for omission and commission errors. These task instructions led to significantly faster RTs for Go trials in Exp 2 than in Exp 1 ($t_{55} = 4.57, p = 0.00003$). Again we demonstrate significantly better remember accuracy for Go- vs. NoGo-items ($t_{25} = 2.85; p = 0.009$; Figure 15A). However, a repeated measures ANOVA on remember accuracy with within-subjects factor response type (Go, NoGo) and between-subjects factor experiment (Exp1 No Reward, Exp 2 Reward) did not show a significant interaction ($F_{1,55} = 12.65; p = 0.91$). These results suggest that reward anticipation is unlikely to account for the observed action-induced memory enhancement.

3.4.4 Action induced memory enhancement is not dependent on time stimulus presentation time window.

Inhibition during Go/NoGo tasks is linked to changes in the amplitude and topography of different waveforms of event-related potentials peaking at ~200-300 ms (Falkenstein et al., 1999; Gonzalez-Rosa et al., 2013; Kiefer, Marzinzik, Weisbrod, Scherg, & Spitzer, 1998) . To provide further evidence that the mnemonic difference in memory performance between Go and NoGo associated stimuli results from an action induced memory enhancement and not from a NoGo-induced (action inhibition) encoding impairment, Exp 3 employed a variable temporal asynchrony between cue-frame and grayscale picture presentation. In this experiment, grayscale pictures for both conditions (Go and NoGo) were presented during one of 3 consecutive time windows of 250 ms (0-250, 250-500, 500-750 ms; Figure 16A) with the frame-cue presented from 0-750 ms. Importantly, an inhibitory account of NoGo-induced encoding disruption would predict that poorer NoGo than Go memory would be most pronounced in the earliest stimulus presentation window (0-250ms), as this corresponds to the temporal profile of inhibition response electrophysiological activity (*e.g.*, the N2 component). Directly contradicting this account, Go item memory was better than NoGo item memory at all stimulus presentation windows (Figure 16B) with similar reaction time (RT) distributions for the 3 windows (Figure 16C).

In a first analysis, collapsing over presentation time window, we replicate a significant effect of motor response on subsequent remember accuracy ($t_{37} = 3.28$; $p = 0.002$, Figure 15A). Critically, a repeated measures ANOVA with factors memory

performance (remembered Go, NoGo) and time window of presentation (0, 250 or 500ms) showed no significant interaction ($F_{24.615,73.334} = 0.22$; $p = 0.80$). This suggests that the effect of voluntary movement/withholding movement on subsequent memory does not exclusively occur at a particularly early stage of the inhibitory process (Figure 16B). We note that Go-associated memory is greater than NoGo memory even when stimuli are presented 500 ms after cue frame onset, which is later than all RTs for this stimulus type (Figure 16C). Although other NoGo-related ERPs, occurring later than the N2, have been described, the results of Exp 2 together with the observed lack of NoGo-item memory modulation on the basis of preceding Go trials, provide evidence against inhibition-induced memory impairment.

Figure 16. Experiment 3. Experimental design and behavioural results. (A) Experimental design of Exp 3. The colored background indicating Go or NoGo response requirement was presented for 750ms while grayscale objects were presented for 250 ms on the center of the screen in either one of 3 possible onset times: 0, 250 or 500 ms. (B) Recognition memory for remembered items corrected by false alarms for each condition Go/NoGo and the time window of presentation (250/500/750ms). (C) Histograms for the mean RTs across participants for Go condition at each time window of presentation.

3.4.5 Action-induced episodic memory enhancement is associated with increased Locus Coeruleus BOLD activity coupled with Parahippocampal Gyrus.

Our behavioral studies were predicated on the hypothesis that taking action would boost episodic memory via interactions between the noradrenergic system and medial temporal lobe memory circuits. To test this hypothesis, we conducted a functional

magnetic resonance imaging (fMRI) study. First, we performed a behavioral pre-fMRI experiment (Exp 4) similar to Exp 1 but with presentation duration of 250ms (frame-cue and picture presented simultaneously). Exp 4 simply ensured that robust memory enhancement for Go vs. NoGo stimuli is observed at this shorter presentation time, employed so as to minimize saccades, which not only lead to spurious BOLD effects (Kimmig et al., 2001) but also represent another type of action that increases LC activity in non-human primates (Kalwani et al., 2014). The results of Exp 4 once more replicated the main finding from Exp 1-3 (better memory for Go vs. NoGo items ($t_{21} = 2.26$; $p = 0.03$; Figure 15A).

The task employed in the context of fMRI scanning (Exp 5) was identical to Exp 4. Behaviorally, although there is a remember advantage for Go vs. NoGo stimuli, this effect was not significant ($t_{20} = 1.41$; $p = 0.17$). With respect to fMRI results, both the Go vs. NoGo comparison (Figure 17A, Table 5) and the opposite test (Figure 17B, Table 6), revealed cortico-subcortical networks previously shown to be involved in action and response inhibition (Aron, 2007; Simmonds, Pekar, & Mostofsky, 2008), respectively. As predicted, parahippocampal activation was observed in the R vs. F, subsequent-memory comparison (Figure 18D and F; Table 7) as has been shown to be engaged during episodic memory formation (Brewer et al., 1998; Kirchhoff et al., 2000).

Figure 17. fMRI Go/NoGo main effects. (A) In the left side significant Go vs. NoGo main effect in left premotor motor cortex ((-28,0,66); $Z = 3.91$; $p < 0.001$ unc.) and the right panel shows the parameter estimates for that activation. (B) Significant NoGo vs. Go main effect in STN (6, -18, 2; $Z = 5.04$, $p < 0.001$ FEW-corrected; STN localized using the probabilistic atlas mask of (Keuken et al., 2014).

Structure	BA	Left/Right	MNI Coordinates			Zscore
			X coor	Y coor	Z coor	
Caudate (tail)	-	L	-16.0	-24.0	18.0	4.31
Superior Parietal Lobule *	5	L	-30.0	-46.0	68.0	4.16
Anterior Lateral	40	R	56.0	-32.0	54.0	4.00
Premotor Cortex	6	L	-28.0	0.0	66.0	3.91
Postcentral Gyrus	7	R	4.0	-56.0	72.0	3.86
Caudate (body)	-	R	8.0	0.0	22.0	3.83
Cuneus	18	R	2.0	-98.0	18.0	3.72
Anterior Lateral	2	L	-56.0	-30.0	52.0	3.70
Postcentral Gyrus	2	L	-66.0	-22.0	28.0	3.55
Cuneus	19	R	2.0	-94.0	28.0	3.55
Postcentral Gyrus	7	L	-14	-50	74	3.37

*Table 5. Go vs. NoGo fMRI effects. Data thresholded at $p < 0.001$ uncorrected. *FWE-corrected for the whole brain cluster level $p < 0.05$. Activations at peak level with more than 5 voxels cluster.*

Structure	BA	L/R	MNI Coordinates			Zscore
			X coor	Y coor	Z coor	
Subthalamic Nucleus*	-	R	6.0	-18.0	-2.0	5.04
Subgenual and Ventral Anterior	32/25	L	-8.0	20.0	-10.0	4.72
Orbitofrontal Cortex*	47	R	24.0	16.0	-18.0	4.57
Hippocampus	-	R	30.0	-12.0	-26.0	4.52
Posterior Cingulate Gyrus*	23	L	-4.0	-54.0	22.0	4.48
Middle Occipital Gyrus	18	L	-28.0	-100.0	0.0	4.37
Superior Occipital Gyrus	19	L	-24.0	-86.0	44.0	4.26
Entorhinal Cortex	28	L	-18.0	-18.0	-24.0	4.21
Superior Temporal Sulcus	22	L	-40.0	-54.0	20.0	4.20
Putamen*	-	L	-22.0	10.0	0.0	4.09
Postcentral Gyrus	3	R	46.0	-22.0	66.0	4.04
Middle Temporal Gyrus*	21	L	-58.0	-24.0	-14.0	4.04
Inferior Temporal Gyrus*	21	R	60.0	-6.0	-18.0	4.02
Superior Occipital Gyrus	19	R	46.0	-76.0	38.0	4.01
Middle Temporal Gyrus/Temporal	38	L	-36.0	12.0	-42.0	4.01
Middle Occipital Gyrus*	19	R	44.0	-84.0	10.0	4.00
Middle Occipital Gyrus	18	L	-42.0	-90.0	6.0	3.98
Superior Parietal Lobule	7	L	-44.0	-72.0	48.0	3.94
Hippocampus	-	R	22.0	-20.0	-8.0	3.94
Caudate (body)	-	L	-10.0	4.0	10.0	3.94
Supplemental Motor Area	6	L	-6.0	-28.0	62.0	3.93

Superior Frontal Sulcus	9	R	26.0	38.0	40.0	3.93
Premotor Cortex	6	R	60.0	0.0	38.0	3.90
Angular Gyrus	39	R	44.0	-56.0	24.0	3.89
Middle Temporal Gyrus/Temporal	38	R	40.0	16.0	-36.0	3.86
Inferior Frontal Gyrus	47	L	-40.0	32.0	-16.0	3.85
Supplemental Motor Area*	6	R	10.0	-36.0	62.0	3.85
Superior Temporal Gyrus	41	R	54.0	-24.0	8.0	3.75
Cerebellum	-	L	-14.0	-56.0	-30.0	3.73
Fusiform Gyrus	37	L	-26.0	-42.0	-16.0	3.70
Lateral Occipital Gyrus	19	L	-18.0	-96.0	30.0	3.69
Middle Occipital Gyrus*	37	R	48.0	-70.0	0.0	3.68
Middle Temporal Gyrus	21	R	46.0	8.0	-38.0	3.65
Clastrum	-	R	32.0	-18.0	16.0	3.62
Medial Frontal Gyrus	6	R	14.0	-12.0	50.0	3.62
Lateral Occipital Gyrus	19	R	26.0	-96.0	24.0	3.61
Uncus	38	R	26.0	12.0	-28.0	3.59
Orbitofrontal Cortex	47	L	-28.0	32.0	-12.0	3.58
Lingual Gyrus	18	R	18.0	-66.0	-6.0	3.58
Inferior Temporal Gyrus	20	R	42.0	-8.0	-36.0	3.58
Precentral Gyrus	6	L	-60.0	-6.0	30.0	3.58
Inferior Temporal Gyrus	20	L	-42.0	-6.0	-38.0	3.56
Orbitofrontal Cortex	11	L	-34.0	42.0	-12.0	3.53
Inferior Temporal Gyrus	20	L	-58.0	-24.0	-28.0	3.52

Posterior Insula	13	L	-42.0	-40.0	22.0	3.52
Precentral Gyrus	43/6	L	-58.0	-6.0	18.0	3.52
Posterior Insula	13	R	42.0	-28.0	20.0	3.52
Fusiform Gyrus	19	R	28.0	-64.0	-8.0	3.50
Posterior Insula	13	L	-38.0	-26.0	18.0	3.46
Fusiform Gyrus	37	R	34.0	-52.0	-12.0	3.46
Supplemental Motor Area	6	L	-6.0	-14.0	66.0	3.43
Superior Temporal Gyrus	22	L	-60.0	-34.0	6.0	3.43
Precentral Gyrus	6	R	62.0	-2.0	10.0	3.41
Superior Frontal Gyrus	8	L	-20.0	40.0	54.0	3.41
Temporoparietal Junction	39	R	56.0	-68.0	22.0	3.39
Thalamus	-	L	-10.0	-24.0	4.0	3.36
Inferior Temporal Sulcus	20	R	44.0	0.0	-26.0	3.33
Anterior Cingulate Gyrus	10	R	12.0	46.0	20.0	3.32
Superior Temporal Gyrus	22	L	-46.0	-20.0	0.0	3.29
Middle Temporal Gyrus	21	L	-46.0	10.0	-38.0	3.24

*Table 6. NoGo vs. Go fMRI effects. Data thresholded at $p < 0.001$ uncorrected. *FWE-corrected for the whole brain cluster level $p < 0.05$. Activations at peak level with more than 5 voxels cluster.*

Structure	BA	Left/Right	MNI Coordinates			Zscore
			X coor	Y coor	Z coor	
Middle Temporal Gyrus	21	L	-56.0	-6.0	-18.0	4.63
Caudate (body)	-	R	12.0	-2.0	26.0	3.97
Cingulate Gyrus	24	L	-8.0	-4.0	28.0	3.93
Fusiform	37	L	-26.0	-42.0	-16.0	3.84
Caudate (body)	-	L	-10.0	16.0	16.0	3.82
Parahippocampal Gyrus †	35	L	-24.0	-26.0	-20.0	3.73
Orbitofrontal Gyrus	47	L	-44.0	22.0	-4.0	3.72
Precentral Gyrus	4	R	60.0	-10.0	26.0	3.26

Table 7. Memory (R vs. F) fMRI effects. Data thresholded at $p < 0.001$ uncorrected. Activations at peak level with more than 5 voxels cluster. † SVC using bilateral posterior parahippocampal mask converted to MNI space from Harvard-oxford atlases for fsl $P = 0.05$ (-24 -28 -20).

The primary aim of this fMRI experiment was to derive mechanistic insights into memory enhancement for stimuli paired with action. Testing for an interaction between motor response (Go vs. NoGo) and subsequent memory (R vs. F) identified a significant activation in dorsal pons, in an area consistent with locus coeruleus (Figure 18A and C, Table 8). To increase the robustness of spatial localization of this response to LC, we repeated this analysis using a spatially unbiased infra-tentorial template (SUIT) (Diedrichsen et al., 2011) for nonlinear normalization of cerebellum and brainstem to provide a more accurate intersubject-alignment of the brainstem than whole-brain methods. The motor response by subsequent memory interaction is shown in Figure

18B. A significant action by subsequent memory interaction was again observed in dorsal pons, overlapping with a probabilistic atlas of the LC (SUIT space coordinates (4, -36, -23), $Z = 3.32$, SVC $p_{FWE} = 0.03$), (Keren et al., 2009) (Figure 18B).

LC sends widespread noradrenergic projections to cortical and subcortical structures, including the MTL (for review see Sara, 2009). To determine which regions correlate with LC activity during encoding, we performed a psychophysiological interaction (PPI) analysis (Friston, 2011) to estimate context-specific changes in coupling between the LC and the rest of the brain. Specifically, we tested which regions were functionally coupled with LC under the experimental context of successful encoding between Go vs. NoGo trials. Coupling between LC activity and parahippocampal gyrus (-32,-38,-12), $Z=3.79$, SVC $p_{FWE} = 0.02$) was observed (Figure 18E, Table 9), in a region in close proximity with parahippocampal cortex expressing a main effect of successful object encoding (Figure 18D). This mirrors recent reports of functional LC-parahippocampal coupling associated with memory performance in healthy subjects (Jacobs et al., 2015), and provides evidence for a LC-MTL circuit underlying the Go-induced encoding enhancement we observe. These results suggest that the action evoked memory enhancement is mediated by a possible LC and parahippocampal gyrus circuit underlying. NE release can be triggered by the action, as has been previously shown in animal studies (Bouret & Richmond, 2009; Bouret & Richmond, 2015; Kalwani et al., 2014; Pavlenko & Kulichenko, 2003; Varazzani et al., 2015), reaching MTL target areas promoting memory formation (Cahill et al., 1994; LaBar & Cabeza, 2006; McGaugh, 2000, 2004; Segal & Cahill, 2009; Strange & Dolan, 2004; Strange et al., 2003; Tully et al., 2010). Emotional arousal has been shown to enhance episodic memory via

noradrenergic mechanism engaging the amygdala (Cahill et al., 1994; LaBar & Cabeza, 2006; Roozendaal, Nguyen, Power, & McGaugh, 1999; Segal & Cahill, 2009; Sterpenich et al., 2006; Strange & Dolan, 2004; Strange et al., 2003; Tully & Bolshakov, 2010; van Stegeren, 2008; van Stegeren et al., 2005), similarly as action was found in the present study. Interestingly there is a PET study (Kilpatrick & Cahill, 2003) and fMRI (Dolcos, LaBar, & Cabeza, 2004) in humans showing functional connectivity between the amygdala and parahippocampal gyrus suggesting noradrenaline is targeting parahippocampal gyrus to enhance memory for emotional stimuli.

Figure 18. Go responses during successful encoding engage the noradrenergic system. (A,B,C) LC Activation (Exp5). (A) Interaction between motor response (Go and NoGo) and subsequent memory (Remembered and Forgotten) has been overlaid on a canonical T1 image to show activation in an area of the dorsal pons consistent with LC (2 -28 -16; $Z = 3.38$; $p < 0.001$ unc.). (B) The same interaction, now in SUIT space (-2, -34, -23, $Z = 3.32$ peak level SVC $p_{FWE} = 0.035$) is overlaid on a high resolution atlas template of the human brainstem and cerebellum., with a probabilistic spatial mask (at 1 std) of LC superimposed. (C) Parameter estimates for the BOLD response in LC. Error bars pertain to s.e.m. (D,E,F) Parahippocampal Activation (Exp5). (D) Parahippocampal activation results of the comparison between remember vs. forgotten (-24 -26 -20; $Z = 3.73$, SVC $p_{FWE} = 0.05$). (E) Parahippocampal activation (-32, -38, -12; $Z = 3.79$; SVC $p_{FWE} = 0.02$) result of a PPI analysis of the LC activation in the interaction between motor response and memory context. (F) Parameters estimate for the BOLD response of the activation observed for comparison between remembered and forgotten.

Structure	BA	Left/Right	MNI Coordinates			Zscore
			X coor	Y coor	Z coor	
Locus coeruleus	-	R	2	-28	-16	3.38

Table 8. Interaction Go/NoGo vs. subsequent memory fMRI effects. Data thresholded at $p < 0.001$ uncorrected.

Structure	BA	Left/Right	MNI Coordinates			Zscore
			X coor	Y coor	Z coor	
Fusiform	37	L	-44.0	-40.0	-14.0	4.05
Parahippocampal †	37	L	-32.0	-38.0	-12.0	3.79

Table 9. PPI of the interaction Go/NoGo vs. subsequent memory fMRI effects. Data thresholded at $p < 0.001$ uncorrected. † SVC using bilateral posterior parahippocampal mask converted to MNI space from Harvard-oxford atlases for $fsl P = 0.02$ (-32 -38 -12).

3.4.6 Pupil dilation also reveal action induced episodic memory enhancement as a proxy measure of LC activation.

Our fMRI results suggested that the enhancement of episodic memory by motor action results from noradrenergic LC responses that upregulate memory encoding processes in the MTL. To provide a second, independent index of LC activity during Go-induced encoding enhancement, we next performed the same Go/NoGo memory paradigm while recording pupil diameter responses (Exp 6). Pupil diameter has been shown to be a reliable, indirect index of LC activation, positively correlating with LC firing rates in

non-human primates (Gilzenrat et al., 2003; Gilzenrat et al., 2010; Jepma & Nieuwenhuis, 2011; Joshi et al., 2016; Rajkowski, Kubiak, & Aston-Jones, 1993) and with BOLD activity in human LC (Alnaes et al., 2014; Gilzenrat et al., 2010; Murphy et al., 2014; Murphy, Robertson, Balsters, & O'connell, 2011b) (see Chapter 2.2.1). We therefore expected that the pupil-derived index of LC activation would relate to memory performance and movement in the same way as that observed with fMRI scanning (Figure 19).

The behavioral results of Exp 6 again show better remember accuracy for stimuli paired with Go vs.NoGo responses ($t_{27} = 2.75$, $p = 0.01$) (Figure 15A, Table 3). To test for an interaction between encoding and button press in pupil diameter, the raw pupil responses (Figure 19A) were z-scored and submitted to a general linear model (GLM) using a basis function approach. Stimulus-locked pupillary responses were modeled with two basis functions, one pertaining to the light-reflex and a later cognitive component, as recently described (de Berker et al., 2016). The Erlang gamma function suggested in (Hoeks & Levelt, 1993) was used for the later cognitive component and the earlier visual component was parameterised by fitting to the pupil responses at encoding to subsequent familiar (K) responses, as statistical inference was not made on these trials. For each subject, parameter estimates for regressors convolved with the cognitive basis function pertaining to our conditions of interest (GoR, GoF, NoGoR and NoGoF) were entered into a 2 by 2 ANOVA. Go responses evoked greater pupil dilation (main effect of Go vs. NoGo, $F_{1,27} = 17.78$; $p = 0.0001$), as is clear from the raw pupil traces, where an initial pupil constriction is observed, due to the light-reflex to stimulus presentation, followed by a later differential dilation (Figure 19A), in line with

previous observations in human (Privitera et al., 2010) and non-human primates (Varazzani et al., 2015). Critically, a significant interaction between response type (Go vs. NoGo) and subsequent memory (R vs. F) is observed ($F_{1,27} = 4.21$; $p = 0.05$). As predicted from the LC activation in Exp 5, this interaction reflects greater pupil dilation to stimuli paired with Go responses that are subsequently remembered (Figure 19 C and D). These results derived from using pupil diameter as a proxy measure of LC activation, reinforce our fMRI evidence that Go-induced encoding enhancement is mediated by the noradrenergic system

Figure 19. Go responses during successful encoding engage the noradrenergic system II. Pupillary responses during successful encoding are modulated by Go responses (Exp 6). (A) Raw pupil diameter relative to baseline change measures averaged over participants (shaded error bars pertain to s.e.m.). (B) The Erlang gamma function (Hoeks & Levelt, 1993) for the earlier visual component parameterised by fitting to the pupil responses at encoding to subsequent familiar (K) responses. Average across participants of z-scored k responses in blue and z-scored fitted gamma responses using parameters n and t_{max} results of `fmincon` MATLAB function in black. (C) Parameter estimates for the cognitive aspect of the pupil responses for GoR, GoF, NoGoR, NoGoF conditions (error bars pertain to residual error of the model). (D) Parameter estimates for the differences of the relative pupil dilation/constriction for the interaction between motor response (Go/NoGo) and subsequent memory (R,F) for the cognitive aspect of the pupil dilation.

3.4.7 Action-induced episodic memory enhancement is modulated by emotion

The results of Exp 5 and 6 demonstrate involvement of LC in Go-induced memory enhancement, indicative of an underlying noradrenergic mechanism. A NE mechanism

has also been shown to underlie enhanced memory for emotionally negative relative to neutral stimuli (Cahill & Alkire, 2003; LaBar & Cabeza, 2006; McGaugh, 2000, 2004; Segal & Cahill, 2009; Strange & Dolan, 2004; Strange et al., 2003; Tully et al., 2010; van Stegeren, Wolf, Everaerd, & Rombouts, 2007). Thus, if “Go” and “emotionally aversive” induced memory enhancements are mediated by a NE mechanism, then a novel hypothesis can be derived stating that Go-induced memory enhancement is modulated by the emotional nature of the stimulus presented simultaneously with movement. This rationale is based on the inverted-U relationship between arousal (noradrenergic activity) and cognitive performance, i.e., the Yerkes-Dodson law (Yerkes & Dodson, 1908). That is, if during memory encoding there are two psychological parameters that increase noradrenergic drive (emotion and voluntary movement), these effects may influence encoding performance in a predictable way (Figure 20A). Thus, Exp 7 was identical to Exp 4 except that, instead of grayscale pictures of objects, participants were presented with an equal number of neutral and emotional color scenes from a standardized database (Lang, Bradley, & Cuthbert, 2008) with cue to Go or NoGo again indicated by a blue/yellow frame. A surprise recognition test was performed after a 24h delay, instead of the 1h interval in all previous experiments, as the enhancing effect of emotion on memory is more evident at this longer time interval (Anderson, Yamaguchi, Grabski, & Lacka, 2006; Hamann, Ely, Grafton, & Kilts, 1999; Kleinsmith & Kaplan, 1963; Ritchey, Dolcos, & Cabeza, 2008; Sharot et al., 2007; Sharot, Delgado, & Phelps, 2004; Sharot & Phelps, 2004; Sharot & Yonelinas, 2008; Yonelinas & Ritchey, 2015).

Our hypothesis was predicated on Go-induced memory enhancement reflecting noradrenergic activity and a subsequent rightward shift along the inverted-U function for neutral stimuli encoding performance (Figure 20A). We therefore first examined memory for participants showing Go-induced memory enhancement for neutral stimuli (16 of the 21 participants in total). Strikingly, although these participants show Go-induced encoding enhancement for neutral stimuli, this is not observed for emotional stimuli (Figure 20B). The Go-induced decrease in encoding of emotional pictures is in keeping with our predictions based on an inverted-U function (Figure 20B). An emotion (neutral, aversive) by response (Go, NoGo) ANOVA on encoding performance showed a significant interaction ($F_{1,15} = 14.12$; $p = 0.002$), whereas the main effect of response was not significant and that of emotion only showed a trend ($F_{1,15} = 3.86$; $p = 0.07$). Post-hoc t-tests revealed significantly different memory performance between Go Emo and NoGo Neutral ($t_{15} = 2.88$; $p = 0.01$) and NoGo Neutral and NoGo Emo ($t_{15} = -3.83$; $p = 0.002$). The difference between Go vs. NoGo Neutral stimulus encoding ($t_{15} = 7.34$; $p = 0.0001$) is obviously biased by preselection of participants showing this effect. Early findings in rats showed this relationship between NE release as a function of arousal and memory performance following an inverted U shaped in a manner that reflects the Yerkes Dobson arousal curve (Yerkes & Dodson, 1908) (Gold & Buskirk, 1978, 1975, 1976a, 1976b; Gold et al., 1977). These results suggest a novel hypothesis based on previous findings describing memory performance as a function of NE release due to action and emotion following an inverted U-shape curve. As emotional arousal increases: (1) performance corresponding with Emotional stimuli should be on the right part of the curve (NoGo Emotional, Go Emotional) showing higher noradrenergic drive for the condition that involves action and aversive emotion simultaneously (Go

Emotional) worsening memory performance; (2) conversely Neutral stimuli should lie on the left side of the curve (NoGo Neutral, Go Neutral) showing lower noradrenergic drive for the condition not involving neither action nor aversive emotion (NoGo Neutral) worsening memory performance, (3) optimal memory performance should be situated in the middle of the curve corresponding with moderate level of emotional arousal and NE release driven by only one NE mediator either action or emotion (Go Neutral, NoGo Emotional).

Figure 20. Go-induced encoding enhancement is modulated by emotion. (A) Schematic “inverted-U” relationship between encoding performance and norepinephrine (NE) level, with putative locus of Go and NoGo encoding on this curve indicated. We hypothesized that emotion would shift memory scores to the right. (B) and (C) Recognition memory for remembered items (R) corrected for false alarm rates for GoNeu, NoGoNeu, GoEmo and NoGoEmo conditions and same schematic depicted in (A) for participants that shows go-induced memory enhancement for the neutral stimuli (N = 16) (B) and those that do not (N = 5) (C). * ($P < 0.05$), ** ($P < 0.01$), *** ($P < 0.001$).

3.4.8 Action-induced episodic memory enhancement depends on arousal

Across all experiments we observed, at a group level of statistical inference, a consistent memory advantage for stimuli requiring a Go response at encoding. However, the advantage was not observed in all subjects. Interestingly, in Exp 7 those participants that do not show Go-induced memory enhancement for neutral stimuli ($N = 5$), actually show better memory for NoGo neutral pictures (Figure 20C). If a Go-induced release of NE impairs memory in these participants, this would be compatible with these participants operating more to the right of the inverted-U function of arousal, (i.e., they were in a state of higher arousal than other participants during the course of the experiment; Figure 20C). Again we find an opposite pattern for Go/NoGo effects on emotional stimuli (Figure 20C). Indeed, a non-parametric Friedman test that showed an interaction between emotion and motor response significant at trend ($\chi^2(3)=7.41$; $p = 0.06$).

The results of Exp 7 provided a putative explanation for not observing memory advantage for stimuli requiring a Go response at encoding for every subject: for participants with a certain degree of arousal, further Go-evoked NE release would be detrimental to encoding performance. To specifically test this explanation, we examined a measure of arousal derived from pupillary measures recorded in Exp 6. The light-reflex (pupil constriction in response to light) shows reduced amplitude in patients with generalized anxiety (Bakes, Bradshaw, & Szabadi, 1990), and is reduced in healthy individuals in the context of arousal produced by pain expectation with the decrease of the light reflex response, but not the increase in the initial diameter of the pupil,

correlating with increased subjective anxiety (Bitsios, Szabadi, & Bradshaw, 1996). We therefore calculated the light-reflex amplitude for all participants in Exp 6 by averaging across all trials during encoding for each subject. (Figure 21) shows pupil response as an average function for two groups: the 22 participants completing Exp 6 who showed enhanced memory for Go vs. NoGo stimuli, and the remaining 6 participants who did not. There is a reduction in light-reflex amplitude in the participants not showing Go-induced memory advantage ($t_{10.747} = -2.23$; $p = 0.048$), supporting our explanation that these individuals have a higher level of arousal during encoding, which negates the mnemonic benefit afforded by Go-induced LC activity.

Figure 21. Reduced constriction due to light reflex for participants that do not show Go induced memory enhancement. Average pupil diameter change relative to baseline is plotted for two groups: the 22 participants completing Exp 6 who show enhanced memory for Go vs. NoGo stimuli (blue), and the remaining 6 participants who do not (light blue).

3.4.9 Speed of response and Go-induced memory enhancement

There is evidence suggesting LC activation is locked to the action response in the monkey but only within the task context. There is no LC response during movements that are not cued (Bouret & Richmond, 2015; Kalwani et al., 2014). This evidence make it difficult to extrapolate our observation of an action-induced memory enhancement driven by noradrenergic engagement to “spontaneous” movements –such as walking, gestures, - which not require action to specific cues.

Interestingly, in all experiments, subjects were required to make button presses as fast as possible. This was necessary in order to obtain a dissociation between commission errors and memory performance due to history of number of preceding Go stimuli on NoGo trials (Figure 15C), important for ascribing the memory difference between the two response types to a Go-induced memory enhancement rather than a NoGo-induced memory impairment. This speeded response instruction could call into question the generalizability of our results to non-speeded movements. However, we show within-subjects, that speed of response (RT) did not differ between subsequently remembered vs. forgotten stimuli (Figure 15B), and did not interact with emotion in Experiment 7 (Table 10). By examining the relationship between RT and Go-induced memory enhancement across subjects, we show a positive correlation between them, suggesting that the slower the button press the more memory enhancement for the Go condition compared with the NoGo ($r = 0.3743$, $p < 0.0001$) (Figure 22). If this Go-induced memory enhancement is mediated by noradrenergic drive, this is in line with results in monkeys showing LC firing aligned with the onset of the action regardless of reaction

times (Bouret & Richmond, 2009; Bouret & Richmond, 2015; Clayton et al., 2004). Thus, the speeded response requirement might not be necessary to observe this memory enhancement for voluntary movements meaning this action induced memory enhancement could be dissociated from the speeded response engagement.

Figure 22. Recognition memory for remembered (R) items corrected by false alarms for the difference between Go and NoGo conditions vs. the mean reaction time for each subject of each experiment in different colors.

T test RT Emotional vs Neutral	Subjects
$t_{20} = -0.97$; $p = 0.34$	All
$t_{15} = -1.18$; $p = 0.26$	R Go>NoGo Neutral Pictures(N=16)
$z = -1.21$; $p = 0.22$	R Go<NoGo Neutral Pictures(N=5)
RT Interaction Emotion vs Memory	Subjects
$F_{1,20} = 0.27$; $p = 0.61$	All
$F_{1,15} = 0.14$; $p = 0.71$	R Go>NoGo Neutral Pictures(N=16)
Friedman $\chi^2(3) = 7.32$; $p = 0.06$	R Go<NoGo Neutral Pictures(N=5)

Table 10. Exp7 Statistics for reaction times (RT).

3.5 Discussion

Over a series of 7 experiments we made a number of observations: (1) an episodic memory improvement by taking action was observed rather than an episodic memory impairment due to action inhibition; (2) this memory enhancement is not mediated by reward anticipation; (3) this action-induced memory enhancement is accompanied by an increase in LC BOLD activity, confirmed by pupil dilation as a proxy measure of LC activation, suggesting a noradrenergic mechanism underlying; (4) action-induced memory enhancement interacts with the emotional content of encoded material suggesting that both action and emotion engage the noradrenergic system.

Over a series of behavioral experiments, dissociating the action from the content of the memory, we showed that not only enactment, as others have previously suggested (Engelkamp & Cohen, 1991; Engelkamp, Zimmer & Biegelmann, 1993; Zimmer, 2001), but also action performance, completely unrelated with the encoded content, can boost episodic memory. Furthermore we provided converging evidence from fMRI and pupilometry measures that this action-induced episodic memory enhancement is mediated by the noradrenergic system. Given the established role of the adrenergic system in modulation of memory for emotional experiences (Cahill et al., 1994; LaBar & Cabeza, 2006; McGaugh, 2000, 2004; Segal & Cahill, 2009; Strange & Dolan, 2004; Strange et al., 2003; Tully et al., 2010) we further assessed noradrenergic role in the action-induced memory enhancement, and showed that this is also modulated by emotional arousal. Strikingly, the emotional content of the stimuli interacts with action-driven NE release (suggested in this study) to modulate memory performance in a way

that reflects Yerkes-Dobson law. This mirrors early studies in which levels of arousal of the experimental animal interacted with injected NE dose to modulate memory performance following an U-inverted curve (Gold & Buskirk, 1978, 1975, 1976a, 1976b; Gold et al., 1977).

Our results contradict previous studies providing an alternative explanation to the phenomenon observed here suggesting an action-inhibition memory impairment rather than an action-induced memory enhancement (Chiu & Egner, 2014, 2015). For this purpose it was important to demonstrate that memory for “*inhibition-response*” cued stimuli (i.e., NoGo items) was not modulated by increasing number of preceding “*action-response*” (Go items). As the number of preceding Gos increases the response inhibition mechanisms are more taxed, leading to an increase in commission errors in the context of an speeded response task (Durstun et al., 2002; Thomas et al., 2009) and also implies that NoGo memory would be worsened. Indeed, in the previous study arguing for NoGo-induced impairment, participants committed more no-go errors as “inhibitory load” increased, but by increasing more number of preceding Gos before a NoGo, the authors did not test for the expected increased disruption of memory (Chiu & Egner, 2014, 2015).

The results provided here also argue against reward anticipation mediating the memory boost for concurrent action and encoding. This suggested that dopaminergic involvement is not necessary in order to observe this memory boost mediated by action as proposed in a previous study (Koster et al., 2015). This, together with monkey data showing LC firing aligned with action response in the absence of reward anticipation –

no reward cue or non-rewarded trials- (Bouret & Richmond, 2015; Clayton et al., 2004) argues in favour of the sufficiency of noradrenergic drive to obtain the observed effect.

Going back to the example given in the introduction, the results presented here suggest that the action of taking a book from a shelf can reinforce subsequent memory retrieval of the title of the book compared with merely looking at the book. Using the framework provided here, the commitment to take the book from the shelf can trigger LC activation and subsequent noradrenaline release can target memory areas in the MTL –e.g. parahippocampal gyrus- to promote encoding and facilitate memory formation.

However, further studies in animal models during performance of memory tasks simultaneously recording LC and target memory areas will be necessary to provide more insight about the NE-mediated mechanism suggested in the present work and to better understand electrophysiological mechanisms that promotes memory formation when an action is taken. Given the involvement of the noradrenergic system on the action-evoked memory enhancement we observe, another important question to be addressed by future lines of research is whether blocking NE, via administering a β -adrenergic antagonist, will block the observed memory enhancement and block movement-evoked electrophysiological responses in MTL.

There is early evidence that in dementia of the Alzheimer type (DAT), the rostrocaudal LC length is shorter and LC neuron numbers are reduced compared to controls (Chan-Palay & Asan, 1989). Furthermore, there is growing evidence pointing to the LC being the first brain region where Alzheimer's disease pathology emerges (Braak, Thal, Ghebremedhin, & Tredici, 2011; Mravec, Lejavova, & Cubinkova, 2014). Furthermore,

in Parkinson's diseases (PD), which is primarily a movement disorder but can also produce memory problems. In PD there is a profound (but less appreciated with respect to SN dopaminergic) loss of cells in the locus coeruleus (LC) (reviewed in Cash et al., 1987; Chan-Palay & Asan, 1989; Hely, Reid, Adena, Halliday, & Morris, 2008; Rommelfanger & Weinshenker, 2007; Scatton, Javoy-Agid, Rouquier, Dubois, & Agid, 1983). Interestingly, there is data indicating that norepinephrine metabolism in the LC is subnormal only in demented parkinsonians that explicitly show memory deficits compared to those with no intellectual deterioration (Cash et al., 1987) and anatomic alterations of the LC are more severe in PD with dementia symptoms compared with those that do not have the symptoms (Chan-Palay & Asan, 1989)

Converging evidence presented here supports the relationship between LC and memory, proposing for the first time voluntary movements as a link between them. These results provide a functional framework for potential future rehabilitation strategies using voluntary movements to enhance memory via noradrenergic engagement in early stages of cognitive impairment. Moreover, pharmacotherapies aimed at restoring NE may have important therapeutic potential in patients with memory disorders.

Chapter 4

**Electrophysiological characterization of novelty
response along the human hippocampal long-axis**

Chapter 4a

A potential source between hippocampal head and body. ERPs along the long axis of the hippocampus during a mismatch detection task.

4.1 Abstract

The human hippocampus has been demonstrated to be involved in novelty detection. The majority of functional imaging studies have reported a contribution of the anterior hippocampus to novelty detection, although some studies report novelty responses in the posterior hippocampus. In this study, novelty-evoked ERPs were observed in anterior, middle and posterior hippocampal segments. Critically, however novelty triggered a negative P300 in the head and positive P300 in body and tail. The polarity inversion between head and body suggests a possible generator between these two hippocampal portions. This polarity inversion can also explain the numerous functional studies only reporting anterior involvement and complement previous studies also showing an ERP polarity inversion from anterior to posterior portions of the hippocampus.

4.2 Introduction

The human hippocampus has been demonstrated to be involved in novelty detection with electrophysiological recordings (Fried et al., 1997; Grunwald, Lehnertz, Heinze, Helmstaedter & Elger, 1998; Knight, 1996) and with functional imaging techniques such as Positron Emission Topography (PET) (Köhler, Crane, & Milner, 2002) or Functional Magnetic Resonance Imaging (fMRI) (Kirchhoff et al., 2000; Kumaran et al., 2006).

The majority of functional imaging studies reporting anterior hippocampal responses to novelty (Constable et al., 2000; Dolan & Fletcher, 1997; Haxby et al., 1996; Köhler, Crane, & Milner, 2002; Saykin et al., 1999; Strange, Fletcher, Henson, Friston, & Dolan, 1999b; Tulving et al., 1996). However there are also studies suggesting posterior hippocampal involvement in novelty detection (Kirchhoff et al., 2000; Rombouts, Machielsen, Witter, Barkhof, Lindeboom, & Scheltens, 1997; Stern et al., 1996). However, novelty evoked responses in posterior medial temporal lobe have been also suggested to originate in the parahippocampal gyrus (see Schacter & Wagner, 1999, for review).

Novelty can be defined as detecting mismatches between expectation and experience as an essential mechanism to anticipate upcoming events. This mechanism has been widely studied using oddball paradigms, where the oddball stimuli represent violation of expectation due to its deviance from the prevailing context (Rugg, 1995). There is evidence suggesting a hippocampal role in oddball detection from intracranial (Barbeau et al., 2016; Halgren et al., 1980; Rosburg et al., 2007; Smith et al., 1990) and scalp

(Garrido, Barnes, Kumaran, Maguire, & Dolan, 2015; Knight, 1996) recordings in humans.

Intracranial recordings during oddball tasks in epileptic patients show large event-related potentials (ERP) in the hippocampus related to the unexpected condition with a peak latency between 300 and 600 ms. This hippocampal component has been termed “MTL P300” in reference to the novelty P300, a positive scalp EEG component recorded in similar experimental conditions (Brázdil et al., 2001; Fell et al., 2005; Halgren et al., 1980, 1995; McCarthy et al., 1989). Lesion studies demonstrated that this potential depends on a network including the hippocampus. Posterior hippocampus lesions were associated with a reduction in the ERP amplitude (Knight, 1996). Negative MTL-P300 components have been reported in studies with anterior hippocampal recordings (Barbeau et al., 2016; Brázdil et al., 2001; Grunwald, Beck, Lehnertz, et al., 1999; Halgren et al., 1995; Ludowig et al., 2010; McCarthy et al., 1989), while positive components have been reported for posterior hippocampus recordings (Roman et al., 2005). Moreover, polarity inversions from anterior to posterior hippocampus have also been reported (McCarthy et al., 1989; Rosburg et al., 2007; Smith et al., 1989). Polarity inversion occurs if the source of electrical activity lies between successive electrode contacts.

In the present study, we directly recorded from the hippocampus in patients with intracranial electrodes implanted for pre-surgical evaluation of epilepsy, while performing an oddball task (previously presented in Axmacher et al., 2010a). Analysing contacts along the long axis of the hippocampus, we specifically tested for novelty

responses not only in the anterior part but also in middle and posterior portions of the hippocampus. We used ERPs locked to the onset of expected and unexpected conditions to explore possible polarity inversions along the long axis to provide insight about possible generators and their location within the hippocampus. These direct recordings, with high spatial resolution, can validate novelty evoked responses along the long axis of the hippocampus reported by previous functional imaging studies. By consistently demonstrating polarity inversions of the oddball-evoked ERP within the hippocampus our data suggest possible source for the novelty signal between head and the body of the hippocampus.

4.3 Methods

4.3.1 Epilepsy patients with hippocampal electrodes

Eleven patients with pharmacoresistant temporal lobe epilepsy (eight females; mean age $\pm$ SD: 37.7 ± 11.54 years) participated in the study (see Table 11). Recordings from these patients were performed at the Department of Epileptology, University of Bonn, Germany. The study was approved by the local ethics committee, and all patients gave written informed consent.

MRI scans revealed unilateral Ammons Horn sclerosis in five patients, one presented with loss of gray-white matter differentiation in the left temporal pole, one presented with MRI lesion to the left temporal pole and four showed no visible pathology. Nine out of the eleven patients had bilateral hippocampal depth electrodes that were implanted for diagnostic purposes using a computerized tomography-based stereotactic insertion technique (Van Roost, Dirk; Solymosi, László; Schramm, Johannes; van Oosterwyck, Birgitt; Elger, 1998).

The location of electrode contacts was ascertained by an MRI in each patient. Electrodes (AD-Tech, Racine, WI, USA) had 10 cylindrical platinum-iridium contacts and a diameter of 1.3 mm. Recordings were performed using a Stellate recording system (Stellate GmbH, Munich, Germany). On average, each patient had 5.9 ± 1.4 (mean $\pm$ SD) hippocampal contacts. Eight patients have electrodes in all hippocampal regions, i.e., in Hippocampal Head (HH), Hippocampal Body (HB) and Hippocampal Tail (HT), 3 patients do not have contacts in the hippocampal tail (HT).

Figure 23. a) Schematic of the segmentation criteria for hippocampal region definition: red HH, yellow HB and pink HT on the left. a1) coronal view of the first slice of the hippocampal tail (taken from Malykhin et al., 2007) a2) coronal view of a slice corresponding with $y=-21$ MNI coordinates) showing the uncus apex landmark (red arrow) used for long-axis segmentation (modified from Poppenk, Evensmoen, Moscovitch, & Nadel, 2013). b)-c) Exemplar pre and post MRI of contacts along the long axis of the hippocampus for one patient.

The uncus apex was used as the transition point from HH to HB (Poppenk et al., 2013). Coordinates where the fimbria-fornix was visualized posterior to the pulvinar nucleus was used as the transition from HB to HT and from body to tail (Malykhin et al., 2007). The hippocampal tail was defined from the end of the body to the last posterior slice (Figure 23).

Patient	Exp performed	Sex	Hand- edness	Age (years)	Age (years) at onset of epilepsy	Aetiology	Lesion location	Seizure type (frequency per months)	Drugs dose (mg)	%of visual rejected spikes
21	19/10/2005	M	R	34	-	Symptomatic therapy of refractory epilepsy with complex-focal and secondarily generalised seizures. MR tomographic Ammons Horn sclerosis right side. Medial temporal lobe epilepsy. Morbus Recklinghausen with chiasma glioma. Folate deficient.	Ammons Horn sclerosis right side.	2/month	Levetiracetam 1500-0-1500mg; Clobazam 0-0-5mg; L-Thyroxin 75-0-0µg	0
27	29/05/2006	M	R	28	10 years	Symptomatic epilepsy with simple-partial, complex-partial and secondarily generalised seizures. Suspicion of disorder of the white-grey-differentiation left temporo-mesial. Depressive disorder.	Anterior left temporal lobe.	-	Lamotrogine 200-0-200mg; Clobazam 0-0-5mg	15

30	05/12/2005	F	R	33	-	Therapy refractory epilepsy with complex-partial seizures. MR tomographic Ammons Horn sclerosis left.	Ammons Horn sclerosis left side (left hippocampus).	-	Levetiracetam 1500-0-2000mg; Clobazam 5-0-5mg;	12
36	03/05/2006	F	R	38	-	Cryptogenic temporal lobe epilepsy with complex-partial seizures.	Left temporal (electrodes TL, TBAL, TBPL).	-	Levetiracetam 1500-0-1500mg; Clobazam 5-0-5mg;	10
39	19/08/2006	F	R	48	18 years	Cryptogenic epilepsy with complex-partial seizures.	Particularly left temporo-polar.	-	Lamotrigin 200-0-200mg; Potassium Iodid 200-0-0mg; Clobazam 10-0-10mg	11
41	31/08/2006	F	R	45	-	Cryptogenic focal epilepsy with complex-partial and secondarily generalised seizures with temporal semiology.	Temporal right.	6-8/month	Lamotrogine 50-0-50mg; Zonisamide 100-0-100mg;	16

43	26/07/2006	M	R	46	10 years	Focal epilepsy with complex-partial seizures. MR tomographic Ammons Horn Sclerosis left side. Cortical disorder of differentiation left temporal pole within the gyrus temporalis inferior.	Ammons Horn sclerosis left side.	5/month	Carbamazepine ret. 400-0-800mg; Zonegram 100-0-100mg;	21
45	20/02/2006	F	R	25	6 years	Cryptogenic epilepsy with complex-partial and secondarily generalised seizures. MR tomographic suspicious lesion temporopolar left. Folate deficient.	Temporal left (TLL 5-7).	-	Carbamazepine ret. 400-0-600mg; Folate 5-0-0mg; Opipramol 50-50-50mg;	18
62	09/11/2005	F	R	18	-	Focal epilepsy with complex-partial seizures. MR tomographic Ammons Horn sclerosis left. Cognitive impairment.	Ammons Horn sclerosis left side.	-	Oxcarbazepine 900-0-900mg; Clobazam 5-0-5mg	14
65	03/04/2007	F	R	56	34 years	Cryptogenic epilepsy with right temporomesial starting complex-partial seizures.	Right temporo-mesial.	1 per 3-4weeks	Levetiracetam 1500-0-1500mg; Dilatrend 12.5-0-0mg	31

71	17/05/2006	F	R	29	-	Epilepsy with complex-partial seizures. MR tomographic Ammons Horn sclerosis and dysplasia of the temporal pole right.	Ammons Horn sclerosis right side (TR, TBAR, TBPR).	-	Levetiracetam 1500-0-1500mg; Lamotrogine 150-0-150mg; Clobazam 10-0-10mg;	25
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Table 11. Patient demographic and clinical data

4.3.2 Experimental design

The experiment was conducted across different ~15 minute sessions including familiarization, encoding and retrieval phases (Figure 24). During the familiarization phase, four stimuli were used as “repeated” stimuli, each of which was presented four times randomly. During encoding phases, 112 pictures from two different categories (houses or faces) were presented. 72% of the stimuli were unique “expected” items of one of the two categories, 14% of the stimuli were unique “unexpected” items from the alternative category presented as expected - 14% of the trials were “repeated” trials from the same category of expected items but they were studied at familiarization phase and were also repeated throughout the experiment. During encoding each trial was presented for 2500ms with a 1500ms inter-trial interval. To ensure subjects were actively participating and attending the stimuli, they were asked to rate each image as pleasant or unpleasant by pressing one of two mouse buttons with the right hand. The order of all trials was pseudorandomized using an m-sequence (Buračas & Boynton, 2002), with the restriction that unexpected trials could never occur consecutively.

The experiment consisted of eight encoding sessions. Different sets of stimuli were used for each session with the exception of the stimuli used on repeat trials, which were the same in each session. Five out of the eleven patients included in the study completed the eight sessions, four of them completed four sessions, one of them five sessions and one three sessions. In this work only iEEG recordings were analyzed for the encoding phases for the expected and unexpected conditions.

Figure 24. Experimental paradigm (only a Study Phase, (encoding of items), included). A majority of items belonged to one category with respect to background colour and content (expected items; e.g., red faces), while a minority of items were deviant (unexpected items; e.g., green houses). (Modified from Axmacher et al., 2010a).

4.3.3 Recordings

Depth EEG recordings were referenced to linked mastoids, recorded at a sampling rate of 1000 Hz. Trials were visually inspected for artifacts (e.g., epileptiform spikes), and trials with artifacts were excluded from further analysis. In nine out of eleven patients recordings were taken from the nonfocal hemisphere (i.e., contralateral to the epileptogenic focus), to minimize the possibility of artifact contamination. Two unilaterally implanted patients were included, with their recordings carefully cleaned during visual artifact rejection. After artifact rejection, contacts were labelled depending on the hippocampal region they belong to: HH, HB and HT, using the anatomical landmarks described above. Given that we intended to examine differences along the

long axis of the hippocampus, we re-referenced our data to an average reference of all hippocampal contacts.

4.3.4 Event Related potentials analysis

We calculated ERPs for each patient and hippocampal electrodes locked to the onset of the stimuli for expected and unexpected conditions using Fieldtrip toolbox for Matlab (<http://www.fieldtriptoolbox.org>). We defined each trial from 100 ms before the stimulus onset until 2 s after. We removed linear trends from the data per trial and performed a baseline correction (baseline period from -100 to stimulus onset). Data was filtered using a 10 order fir low pass filter with low a pass frequency of 20 Hz. Grand averages across subjects were performed for the different regions (HH, HB, HT) and conditions (expected, unexpected). A cluster-based corrected two-tailed ttest was performed comparing unexpected and expected conditions for each region 1 s after the onset of the stimuli using a maxsum cluster statistic montecarlo method (alpha 0.025, cluster alpha 0.05 and 1000 randomizations).

4.4 Results

We observed a biphasic waveform following stimulus presentation in all three subregions HH HB and HT with its first deflection peaking at ~250ms and a second sustained deflection. Furthermore, we observed a polarity inversion of the ERP between the HH and the HB. That is in the body and tail, we found a positive polarity first deflection, whereas we found a negative polarity in the head (Figure 25). This polarity inversion is consistent across subjects. In Figure 26 the polarity inversion is indicated by a green line and it occurs at the same time for every subject. This first deflection did not yield a significant difference between unexpected vs expected condition, however we found a significant difference between unexpected vs expected condition (cluster based corrected) in the HB (545-645 ms; $p_{clus} < 0.029$) and a significant difference between around 600 ms in the HT being more negative for unexpected condition (457-744 ms; $p_{clus} < 0.018$).

Figure 25. Event Related Potentials (ERPs) along the longitudinal axis of the hippocampus. a) ERPs for expected and unexpected conditions, depicted in blue and red respectively, averaged across regions (HH, HB, HT) and subjects. Significant differences between expected and unexpected conditions were found in the body (545-645 ms ; $p < 0.029$) and the tail (457-744 ms ; $p < 0.0180$). b) Schematic of the hippocampus with the dentate gyrus (DG) visible inside with an electrode array along the long axis. The hippocampus body as well as the uncus and landmark used to define HH end (uncal apex) are indicated. c)–f) Coronal slices showing the hippocampal subfields in the anterior hippocampus. From b) to f) modified from (Zeidman & Maguire, 2016).

Figure 26. ERPs for unexpected condition in red and expected condition in blue for every subject and averaging contacts for each region HH, HB and HT. The green vertical line indicates the polarity inversion.

4.5 Discussion

Human hippocampus has been demonstrated to be involved in novelty detection with electrophysiological recordings (Fried et al., 1997; Grunwald, Lehnertz, Heinze, Helmstaedter & Elger, 1998; Knight, 1996) and with functional imaging techniques such as Positron Emission Topography (PET) (Köhler et al., 2002) or Functional Magnetic Resonance Imaging (fMRI) (Kirchhoff et al., 2000; Kumaran et al., 2006).

There are more functional imaging studies reporting anterior hippocampal responses to novelty (Constable et al., 2000; Dolan & Fletcher, 1997; Haxby et al., 1996; Köhler et al., 2002; Lepage et al., 1998; Saykin et al., 1999; Strange et al., 1999b; Tulving et al., 1996), than studies reporting novelty evoked posterior hippocampal responses (Kirchhoff et al., 2000; Rombouts, Machielsen, Witter, Barkhof, Lindeboom & Scheltens, 1997; Stern et al., 1996). However novelty evoked responses in posterior medial temporal lobe have been suggested to take place in the parahippocampal gyrus (see Schacter & Wagner, 1999 for review).

The results presented in this study show the involvement of the posterior part (HB and HT) of the hippocampal formation during unexpectancy processing as has previously suggested by some functional imaging studies (Kirchhoff et al., 2000; Rombouts, Machielsen, Witter, Barkhof, Lindeboom & Scheltens, 1997; Stern et al., 1996).

We observed the same temporal pattern of the ERPs as in (Axmacher et al., 2010). In this study we used data used in this previous study with overlap of patients. Axmacher and colleagues showed an early positive peak at 186.9 ± 16.7 ms (mean $\pm$ SEM) and a

later negative peak at 481.5 ± 63.3 ms, without specifically looking at spatial location of the electrodes.

Interestingly, we observed a polarity inversion of the ERP components between the head and the body portions of the hippocampus, which suggests the existence of a possible generator between these regions within the hippocampus. This result suggests the existence of a potential dipole –e.g. a sink in the HH and a source in the HB or vice versa- representing transmembrane current flow in neuronal ensembles entering or leaving these two regions.

Consistently, a negative hippocampal novelty P300 has been shown for oddball stimuli (Barbeau et al., 2016; Brázdil et al., 2001; Fell et al., 2005; Grunwald, Beck, Lehnertz, et al., 1999; Halgren et al., 1995; Ludowig et al., 2010; McCarthy et al., 1989; Roman et al., 2005) whereas in the adjacent areas -anteriorly, posteriorly, and superiorly to the hippocampus- the P300 has been shown to be positive (Brázdil et al., 2001; Grunwald, Beck, & Lehnertz, 1999; Halgren et al., 1995; McCarthy et al., 1989) suggesting a local generation of the MTL-P300 within the hippocampus.

All the studies reporting negative MTL-P300 in the hippocampus recorded from anterior portions of the hippocampus (Barbeau et al., 2016; Brázdil et al., 2001; Grunwald, Beck, Lehnertz, et al., 1999; Halgren et al., 1995; Ludowig et al., 2010; McCarthy et al., 1989). One study is reporting a positive MTL-P300 in posterior hippocampus (Roman et al., 2005). However, to specifically find a polarity inversion it is necessary the same referencing of the contacts. Most remarkably though, three of those studies report a polarity inversion from anterior to posterior portions of the

hippocampus, being negative in more anterior portions and positive in posterior (McCarthy et al., 1989; Rosburg et al., 2007; Smith et al., 1989). Our observation of a polarity inversion between HH and HB extends these last studies providing insight about the location of a possible generator.

There is evidence from intracranial recordings in multiple locations of the MTL showing local voltage gradients along the longitudinal axis of the HB and subiculum oriented in opposite directions. Larger amplitudes were observed in posterior portions compared to anterior in the HB and larger amplitudes anterior than middle in the subiculum suggesting that at least two separate generators in the MTL elicit the MTL-P300 potentials: one in the anterior subiculum and one in the posterior hippocampal body (Ludowig et al., 2010). In this work, they analysed electrodes in the anterior half of the subiculum, which is located in between the hippocampal head and body consistent with a possible generator that can be eliciting this polarity inversion between head and body reported in the present study. However it is difficult in current imaging to see subiculum-hippocampal boundary once the electrodes are implanted.

The higher amplitudes observed in the tail in comparison with the rest of the hippocampal formation can be explained by previous work showing novelty evoked responses in posterior medial temporal lobe suggested to take place in the parahippocampal gyrus (see Schacter & Wagner, 1999). The higher amplitudes in the negative peak observed in the hippocampal tail compared to the body and the head could be due to the proximity to the parahippocampal gyrus. Nonetheless, the hypothesis of different sources generating this polarity inversion of the ERPs or for the

higher amplitudes observed in the tail could be further substantiated by a Current Source Analysis (CSD). CSD analysis has been used extensively to localize the pattern of transmembrane current flow in neuronal ensembles calculated as is the second spatial derivative of the local field potential (LFP). Source localization based l2-weighted minimum norm algorithm (wMNE) (Hauk, 2004) methods can also be used for this purpose as used in (Méndez-Bértolo et al., 2016). We conclude that a possible source of unexpected response could be placed in the anterior hippocampus. We hypothesise the posterior region late potential to arise from parahippocampal gyrus.

Chapter 4b

Intracranial EEG correlates of unexpectancy along the long axis of the human hippocampus.

4.1 Abstract

Theta and gamma have been shown to be important oscillations in the hippocampus. However, a systematic evaluation of these frequencies along the long-axis has not been done in humans. This chapter addresses this with several analyses. First we show theta and gamma power increases during novelty responses, with higher power posteriorly. We then show the population theta frequency is constant across the long-axis, although this frequency is slightly reduced for unexpected stimuli. Synchronicity between these subregions along the longitudinal axis at this dominant frequency is increased by unexpectancy. However, using measures that are not confounded by power increases, we observed no modulation of synchronicity by unexpectancy. Lastly we observed that gamma oscillations are not modulated by lower frequencies with decreased frequency from posterior to anterior portion as expected. We only observed a decrease in oscillatory frequency from posterior to middle portions of the hippocampus, however no significant interaction between region and novelty was observed along the long-axis.

4.2 Introduction

The hippocampus is involved in detecting mismatches between expectation and experience as an essential mechanism to react to ever changing environment. Although there is an extensive literature on hippocampal novelty detection (Flicker & Geyer, 1982; Fyhn et al., 2002; Gray, 1982; Jenkins et al., 2004; Knight, & Nakada, 1998; Knight, 1996; Lisman, 1999; Lisman & Grace, 2005; O'Keefe, Nadel, 1978; Rank, 1973; Sokolov, 1990; Strange & Dolan, 2001; Tulving et al., 1996; Vinogradova, 1975b, 2001; Yamaguchi et al., 2004; Yang & Mogenson, 1987), mechanisms underlying novelty detection have yet to be understood in humans.

A novel avenue for understanding hippocampal function is by studying the fundamental role(s) of portions along the hippocampal long-axis. It has been suggested different superimposed patterns of functional organization along the long-axis attending to different criteria: electrophysiology, anatomy, gene expression and function. On one hand, there is a dichotomist functional view of different parts of the hippocampus which associate anterior (ventral) hippocampus with anxiety related behaviors and posterior (dorsal) part of the hippocampus with memory and spatial navigation; on the other hand gene expression studies differentiate 9 functional hippocampal domains with sharply demarcated borders. Finally anatomical and electrophysiological studies show the long axis function organized in gradients. Therefore, a potential framework in which there are superimposed patterns of long axis organization attending to different criteria has been suggested (Strange, Witter, Lein, & Moser, 2014).

In previous Chapter 4a we described evidence for functional MRI data pointing towards an anterior hippocampus role in novelty detection yet we show, for LFP recordings, both anterior, middle and posterior hippocampal responses. This raises the interesting question whether all three subregions show similar oscillatory responses to novelty and if there is a modulation of coupling between subregions in this context.

Oscillations at different frequency bands such as gamma (25-150Hz) and theta (4-10Hz) can be observed in the Local Field Potential (LFP), which are extracellular recordings that providing a measure of average neural activity in a brain region (Buzsáki, Anastassiou, & Koch, 2012). These oscillation have been suggested to play an important role in cognition (Colgin & Moser, 2010; Lisman & Jensen, 2013; Nyhus & Curran, 2010).

Previous work in rodents described a theta and gamma power increase in CA1 and Dentate Gyrus (DG) and theta and gamma coherence increasing along the long axis of CA1 in response to novelty environment (Penley et al., 2013). Thus the theta and gamma input that CA1 receives conveys a more coherent message in response to novelty that may promote successful encoding of novel stimuli (reviewed in Nyhus & Curran, 2010).

In addition, previous study in humans has shown the most pronounced difference between processing of unexpected and expected items in the hippocampus was an early (200–400 ms) increase and later (500–1400 ms) decrease of theta band activity, and an increase between 500–700 ms and 1000–1100 ms in the high gamma (70–90 Hz) frequency range (Axmacher et al., 2010). There is also evidence from iEEG recordings

showing increased low-frequency power (in the slow-theta range) in human hippocampus during associative prediction violations in a mismatch detection task (Chen, Dastjerdi, Foster, LaRocque, Rauschecker, Parvizi & Wagner, 2013). This early increase in the theta power for oddball responses has been related with the hippocampal MTL-300 -previously shown in Chapter 4a-, the timing of the power increase for target responses seems to correspond to the timing of the negative deflection of the MTL-P300 in the averaged ERPs (Fell et al., 2004)

In this study we employ direct hippocampal recordings, from patient with intracranial electrodes implanted for pre-surgical evaluation of epilepsy, to specifically test for oscillatory responses to examine the electrophysiological correlates of expectancy along the long axis of the hippocampus.

The present study tested the hypothesis that unexpectancy processing would alter theta and/or gamma signals and coupling between them along the long axis of the hippocampus. We expected that not only an increase of theta and gamma power in different regions and an increase of coherence between different regions along the long axis of the hippocampus, hippocampal head (HH), body (HB) and tail (HT), is involved in unexpectancy processing, but also we tested how lower frequencies modulate higher frequency activity.

4.3 Methods

The same patients, hippocampal electrodes and paradigm were used in this chapter as described in Chapter 4a.

4.3.1 Time frequency analysis

We performed an induced time frequency analysis using the Fieldtrip toolbox in Matlab. In order to inspect conditions separately, a baseline correction was applied from -100ms to 10ms. For comparing conditions no baseline correction was applied. For the lower frequencies we used a Hanning taper method with a fixed window length of 500ms from 1 to 34 Hz in steps of 2 Hz. For the higher frequencies, from 32.5 to 150Hz in 2.5 Hz steps, a multitaper method was used with a frequency smoothing of 10 Hz and a sliding time window of 400 ms. Data was first filtered (high pass filter cut-off 2 Hz, notch-filter 50 Hz), demeaned and detrended. Trial-by-trial automatic artifact rejection was then performed in the frequency domain; the maximum of the logarithm of power per frequency bin was calculated and all trials with mean power 3 standard deviations above or below the mean were excluded from further analysis. Subsequently, data from contacts within each of the three different hippocampal long-axis portions defined (HH, HB and HT) were averaged for each patient. Regions were then grand averaged across patients. A two tailed t-test between Unexpected and Expected condition was performed for each region. Next, a cluster based correction was performed using a maxsum cluster statistic montecarlo method with a cluster alpha 0.05 and alpha of 0.025 and 1000 randomizations. A one way ANOVA was calculated on 8 patients who preserve all 3 hippocampal subregions (3 did not have contacts in the tail) on the difference of the

Unexpected and Expected condition. Similarly, a cluster based correction was applied with a maxsum cluster statistic montecarlo method with a cluster alpha of 0.05 and alpha of 0.025 and 1000 randomizations.

4.3.2 Cross Frequency Coupling

4.3.2.1 Phase Amplitude Coupling.

We uses Phase Amplitude Coupling method described in (Jiang et al., 2015). This method involves three steps, first the estimation of the temporal evolution of the power of the signal (envelope) at higher frequencies Υ , then the estimation of the Fourier transform and cross-spectral densities and finally quantification of the CFC using coherence.

For calculating the power of the signal $x[n]$ as a function of time $v_{x\Upsilon}[n]$ in the gamma band Υ , for each frequency each trial is first segmented into sliding windows of M samples long to reduce spectral leakage and multiplied by a Hanning taper h . The length of the sliding time window can be chosen to be decreasing with increasing frequency (like the case of Morlet wavelets), about w cycles long with respect to the frequency Υ ($M = w \cdot Fs/\Upsilon$) [23]

$$v_{x\Upsilon}[n] = \frac{1}{Fs} \left| \sum_{m=1}^M h[m] x_{\Upsilon}[n + m - M/2] e^{-j \frac{2\pi \Upsilon m}{Fs}} \right| \quad [23]$$

Next, $x[n]$ and $v_{x_Y}[n]$ are segmented into a set of S successive segments $(x^S[n], v_{x_Y}^S[n])$ with l overlapping time points. There will be k time points in each segment. Using a standard Fast Fourier Transform (FFT) algorithm, the complex representations are calculated after applying a Hanning window [24][25].

$$X^S = FFT(h^T x^S, n_{FFT}) \quad [24]$$

$$V_{x_Y}^S = FFT(h^T v_{x_Y}^S, n_{FFT}) \quad [25]$$

Where n_{FFT} defines the frequency resolution. Then the Cross Spectra is calculated as follows [26]:

$$\xi^{YS} = X^S (V_{x_Y}^S)^* \quad [26]$$

Where $*$ denotes the complex conjugate. Finally CFC measure is calculated quantifying coherence between signals x^S and $v_{x_Y}^S$ as follows [27]:

$$CFC(Y, \theta) = \frac{|\sum_{s=1}^S \xi^{YS^2}|}{\sqrt{\sum_{s=1}^S |X^S|^2 \sum_{s=1}^S |V_{x_Y}^S|^2}} \quad [27]$$

With frequencies $\theta \in \left\{0, \frac{F_s}{n_{FFT}}, \dots, \frac{F_s}{n_{FFT}} \left(1 - \frac{1}{n_{FFT}}\right)\right\}$ (for more details see Jiang et al., 2015)

We used this method with code provided by the authors with our data per every subject and contact. We defined the trials from 100ms before the onset of the stimulus to 2s after. We used the following values for the parameter of interest: $w = 5 \text{ cycles}$; $F_s = 1000$; $n_{FFT} = 2.048$; $l = .25$; $k = .5$; $\gamma \in [30, 150]\text{Hz}$; $\theta \in [1, 30]\text{Hz}$.

4.3.2.2 Envelope Method

We used the envelope method in which the power spectrum of the envelope in the gamma band was calculated to inspect lower frequencies modulating gamma envelope. For calculating the power signal at γ frequency as a function of time $v_{x\gamma}[n]$ we used the approach described previously in [23] with parameters $M = w \cdot F_s/\gamma$ ($w = 5 \text{ cycles}$; $F_s = 1000 \text{ samples/second}$; $\gamma = 80 \text{ Hz}$). To estimate the time frequency of the envelope, we used a Hanning taper method with a fixed window length of 500ms from 1 to 34 Hz in steps of 2 Hz. Then we averaged the result per region. A two tailed ttest between Unexpected and Expected condition was performed for each region. A cluster based correction was performed using a maxsum cluster statistic montecarlo method with a cluster alpha of 0.05 and alpha of 0.025 and 1000 randomizations. With this method it is possible to observe modulations of activity in higher frequency bands even where there is a suppression of activity in the lower frequency range (for more detail see Chapter 2).

4.3.3 Frequency sliding

In order to determine the peak theta frequency we used the frequency sliding method suggested by (Cohen, 2014) which estimates the instantaneous frequency of a dynamical oscillation system based on the change in instantaneous phase per unit of time. This method therefore allows assessment of temporal fluctuation in peak frequency. We calculated the instantaneous frequency per contact per patient and the average across regions and subjects. Then we performed for each region a cluster-based corrected two tailed t-test analysis between conditions along time to identify significant differences in the frequency peak along time with expectancy. Then averaging this value in a time window from 200-900 ms post stimulus presentation, we performed an ANOVA to test for an interaction between Expectancy (expected, unexpected) vs region (HH, HB, HT).

4.3.4 Imaginary Coherence and Phase locking value

Two measures of synchrony were calculated both between contacts within hippocampal subregion and between hippocampal subregion. We calculated absolute value of the Imaginary Part of the Coherency (iCoh) with the method suggested in (Nolte et al., 2004) which is insensitive to false connectivity arising from volume conduction (no phase lag between signals). Furthermore we calculated the phase locking value (PLV) (Lachaux et al., 1999) to make sure the coherence values we obtained were not driven by differences in amplitude previously seen in the power spectrum analysis. We calculated for each patient, condition and contact the absolute value of the iCoh and PLV at the theta frequency determined by the sliding method. Given that coherence and

phase locking value measures suffer from bias when comparing conditions with different number of trials (Bastos & Schoffelen, 2015), we randomly selected the number of trials for the expected condition to match the unexpected and averaging across 500 randomizations for each subject. For each subject we ended up with iCoh and PLV measures both for within and between subregion contacts pairs (Table 12) averaged across or within regions. A repeated measures ANOVA with factor expectancy (expected, unexpected) vs within-portion (HH-HH, HB-HB, HT-HT) or between portion (HH-HB, HH-HT, HB-HT) was performed for the imaginary coherence and PLV separately across patients.

	Within subregion			Between subregions		
	HH-HH	HB-HB	HT-HT	HH-HB	HH-HT	HB-HT
P 21	HH1-HH2	HB1-HB2	--	HH1-HB1	--	--
				HH1-HB2		
				HH2-HB1		
				HH2-HB2		

P 27	HH1-HH2	HB1_HB2	--	HH1_HB1	HH1_HT	HB1_HT
	HH1_HH3			HH2_HB1	HH2_HT	HB2_HT
	HH2_HH3			HH3_HB1	HH3_HT	
				HH1_HB2		
				HH2_HB2		
				HH3_HB2		
P 30	HH1_HH2	HB1_HB2	--	HH1_HB1	--	--
	HH1_HH3			HH2_HB1		
	HH2_HH3			HH3_HB1		
				HH1_HB2		
				HH2_HB2		
				HH3_HB2		
P 36	HH1_HH2	HB1_HB2	--	HH1_HB1	HH1_HT	HB1_HT
	HH1_HH3			HH2_HB1	HH2_HT	HB2_HT
	HH2_HH3			HH3_HB1	HH3_HT	

				HH1_HB2		
				HH2_HB2		
				HH3_HB2		
P 39	HH2_HH3	--	--	HH2_HB	HH2_HT	HB_HT
				HH3_HB	HH3_HT	
P 41	HH1_HH2	HB1_HB2	--	HH1_HB1	--	--
	HH1_HH3			HH2_HB1		
	HH2_HH3			HH3_HB1		
				HH1_HB2		
				HH2_HB2		
				HH3_HB2		
P 43	HH1_HH2	HB1_HB2	HT1_HT2	HH1_HB1	HH1_HT1	HB1_HT1
			HT1_HT3	HH2_HB1	HH2_HT1	HB2_HT1
			HT2_HT3	HH1_HB2	HH1_HT2	HB1_HT2
			HT1_HT4	HH2_HB2	HH2_HT2	HB2_HT2

				HT2_HT4	HH1_HT3	HB1_HT3
				HT3_HT4	HH2_HT3	HB2_HT3
					HH1_HT4	HB1_HT4
					HH2_HT4	HB2_HT4
P 45	HH1_HH2	HB1_HB2	HT1_HT2	HH1_HB1	HH1_HT1	HB1_HT1
	HH1_HH3	HB1_HB3		HH2_HB1	HH2_HT1	HB2_HT1
	HH2_HH3	HB2_HB3		HH3_HB1	HH3_HT1	HB3_HT1
				HH1_HB2	HH1_HT2	HB1_HT2
				HH2_HB2	HH2_HT2	HB2_HT2
				HH3_HB2	HH3_HT2	HB3_HT2
				HH1_HB3		
				HH2_HB3		
				HH3_HB3		
P 62	HH1_HH2	HB1_HB2	HT1_HT2	HH1_HB1	HH1_HT1	HB1_HT1
				HH2_HB1	HH2_HT1	HB2_HT1

				HH1_HB2	HH1_HT2	HB1_HT2
				HH2_HB2	HH2_HT2	HB2_HT2
P 65	HH1_HH2	--	--	HH1_HB	HH1_HT	HB_HT
	HH1_HH3			HH2_HB	HH2_HT	
	HH2_HH3			HH3_HB	HH3_HT	
	HH1_HH4			HH4_HB	HH4_HT	
	HH2_HH4					
	HH3_HH4					
P 71	HH1_HH2	HB1_HB2	HT1_HT2	HH1_HB1	HH1_HT1	HB1_HT1
	HH1_HH3			HH2_HB1	HH2_HT1	HB2_HT1
	HH2_HH3			HH3_HB1	HH3_HT1	HB1_HT2
				HH1_HB2	HH1_HT2	HB2_HT2
				HH2_HB2	HH2_HT2	
				HH3_HB2	HH3_HT2	

Table 12. Labels of the channels used for the iCoh and PLV analysis within subregion and between subregion.

4.4 Results

4.4.1 Time frequency

In a previous study Axmacher et al. (2010) showed theta (3–8 Hz) power is first (200–400 ms) increased and later (500–1400ms) decreased during processing of unexpected as compared with expected items in the hippocampus. Higher (70–90 Hz) gamma power is selectively increased in the hippocampus during processing of unexpected items between 500–700 and 1000–1100 ms. Using the same data but specifically looking at spatial localization of the contacts within the hippocampus, we showed the same pattern of power increase and later decrease of the theta power and an increase of the gamma power in the comparison between Unexpected and Expected condition along the long axis (Figure 28). Particularly we observed in the theta band in the comparison between Unexpected and Expected comparison revealed a significant cluster in the HH (3-5Hz, 160-420ms, $p_{clust} < 0.025$), for the HB we found a significant cluster (3-5Hz, 180-380ms, $p_{clust} < 0.012$); and for the HT we found a significant cluster (1-11Hz, 0-450ms, $p_{clust} < 0.001$). For the higher frequencies we found a significant cluster in the comparison between Unexpected and Expected in the HH from (120-750ms, 60-90Hz, $p_{clust} < 0.003$), for the HB (67-112Hz, 60-800ms, $p_{clust} < 0.001$) and for the HT we found a significant cluster from (80-150Hz, 90-1000ms, $p_{clust} < 0.001$) (Figure 27, Table 13).

Freq range	Cluster results	Region		
		HH	HB	HT
Low 2-34 Hz	[tmin,tmax] (ms)	[160 420]	[180 380]	[0 450]
	[fmin, fmax] (Hz)	[3 5]	[3 5]	[1 11]
	p_{clust}	0.025	0.012	0.0009
High 34-150 Hz	[tmin,tmax] (ms)	[120 750]	[60 800]	[90 1000]
	[fmin, fmax] (Hz)	[60 90]	[67 112]	[80 150]
	p_{clust}	0.003	0.0009	0.0009

Table 13. Summary for the cluster based statistical analysis between expected and unexpected conditions per each region. Minimum and maximum frequencies and times for the significant clusters, p values corrected for multiple comparisons.

Figure 27. Time frequency plots for the logarithmic relative change in power between expected and unexpected conditions with the significant clusters that survived correction for multiple comparisons outlined in black. Each region HH, HB and HT in columns and for lower frequencies (0-30Hz) lower row and higher frequencies upper row (30-150Hz)

Figure 28. Time frequency plots for the relative to baseline power change for expected and unexpected conditions (baseline from -100ms to -10ms). Each region HH, HB and HT in columns and for lower frequencies (0-30Hz) lower row and higher frequencies upper row (30-150Hz).

Similarly to what we observe, in previous study has been shown a power decrease from dorsal (posterior) to ventral (anterior) hippocampus (Patel et al., 2012). Inspecting the interaction between regions and expectancy no cluster survived correction for multiple comparisons indicating an absence of significant differences in terms of power along the long axis of the hippocampus during unexpectancy processing. Despite the high power in alpha beta frequencies in the tail no significant effect was found.

4.4.2 Cross Frequency Coupling

One of the aims of the present study was to explore how the lower frequencies modulate higher frequencies. For doing so we first used a Phase Amplitude Coupling (PAC) method. However, this did not reveal any significant PAC between theta phase and gamma amplitude. This may have been due to the later suppression of theta observed in the power spectrum following an unexpected stimulus (see simulation in Chapter 2.3.1.4 and Figure 28). Thus, given the early increase and later suppression of theta power we explored cross frequency coupling in terms of lower frequencies modulating the gamma envelope (envelope method). Using this method it is also possible to look for amplitude modulations in higher frequencies (as it was introduced in Chapter 2). We therefore inspected the time frequency power spectrum of the gamma frequency envelope. A cluster-based permutation test of the comparison between expected and unexpected conditions revealed a broadband significant difference (0-20Hz, 140-740ms, $p_{clust} < 0.001$) modulating an 80Hz envelope in the hippocampal head, a cluster was found in the delta-theta-alpha band for the body (0-14Hz, 276-610ms, $p_{clust} < 0.002$)

and a cluster was found in the delta-theta in the tail (0-6Hz, 420-674ms, $p_{clust} < 0.001$) and in the beta band (14-18 Hz, 500-700ms, $p_{clust} < 0.02$) (Figure 29).

Figure 29. Cross Frequency Coupling results. Power relative change for Unexpected condition compared to Expected of the 80 Hz gamma envelope. For HH, HB and HT portions significant cluster outlined in black

A one way ANOVA on the difference of the power spectrum between conditions (unexpected and expected) with region factor (HH, HB and HT) revealed no significant interaction.

4.4.3 Frequency sliding

Previous work has shown that the frequency of theta oscillations remains the same along the hippocampal long axis in rodents (Patel et al., 2012). On the other hand other authors have demonstrated that Unexpected environments produces a reduction in theta frequency in rodents (Jeewajee et al., 2008). In the present study we performed a

frequency sliding analysis suggested in (Cohen, 2014) to test whether theta peak frequency varies with expectancy along the long axis of the hippocampus.

The frequency sliding analysis revealed no significant change in the theta frequency (4 to 8 Hz) along the long axis as previously shown in (Patel et al., 2012). However, we show a decrease in theta frequency for the unexpected condition of $f \sim 0.05\text{Hz}$, this mirrors results previously found in rodents (Jeewajee et al., 2008) albeit with smaller amplitude of reduction. Inspecting the time course of the frequency peak we found significant cluster in the comparison between Unexpected and expected condition ($p_{clust} < 0.03$) for the HH, for the HB a tendency ($p_{clust} < 0.06$) and for the HT ($p_{clust} < 0.02$) (Figure 30).

Figure 30. Frequency Sliding results for the theta band for each condition (red unexpected, blue expected) and hippocampal region HH, HB and HT. In black significant time clusters that survive correction for multiple comparisons, in grey not significant cluster after correction.

We averaged the frequency value across time for the two conditions and performed a repeated measures ANOVA testing condition (expected, unexpected) by region (HH, HB, HT) across subjects. We did not find an interaction but a main effect of expectancy along the long axis ($F_{1,27} = 27,084$, $p < 0.0001$) (Figure 31).

Figure 31. Average of the frequency peak values along the trial per condition and region across subjects.

4.4.4 Imaginary Coherence and Phase locking value

Performing a repeated measures ANOVA with factors within-portion (HH-HH, HB-HB and HT-HT) and expectancy (expected and unexpected), we show no significant main effect or interaction between hippocampal coherence (or phase locking values) and expectancy for the theta frequency peak within the same hippocampal region during

novelty processing. However, when examining inter-region coupling a repeated measures ANOVA, within-subject factor inter-portion (HH-HB, HH-HT and HB-HT) and expectancy (expected and unexpected) we shows a main effect of expectancy ($F_{1,24} = 7.51$, $p = 0.01$) with higher coherence for the Unexpected condition (Figure 32). This is consistent with previous work in rodents showing that novelty increases theta coherence along the long axis (Penley et al., 2013). We next limited this analysis to the patients in whom head, body and tail contacts were present. The same repeated measures ANOVA, showed only a trend towards a main effect of expectancy ($F_{1,7} = 4.337$; $p = 0.075$).

Figure 32. Theta coupling within and between hippocampal subregions. Left column average across subjects of the Imaginary part of the coherence for the peak theta frequency at 5.5Hz intra and inter region upper and lower figure respectively. Right column same plots for the Phase Locking values at the same frequency peak.

Although the imaginary part of the coherence measures synchrony and limits the confounding effect of volume conduction, it is still affected by amplitude. Thus, PLV analysis was also conducted to test whether the significant main effect in the imaginary coherence was driven by the amplitude being higher for the unexpected condition. Critically, we show in the PLV analysis there is only a trend in the main effect of expectancy ($F_{1,24} = 3.56$; $p = 0.07$). No main effect was observed when this analysis was limited to the patient in whom contacts in every portion were present ($F_{1,7} = 2.67$, $p = 0.1$).

4.5 Discussion

In the current study we observe electrophysiological correlates during unexpectancy processing in terms of an inter-region coherence, within region power increase and a modulation of the gamma envelope by the lower frequency with decreasing frequency band only from posterior to middle portions of the hippocampus.

We first show an early power increase and later decrease in the theta band and gamma power increase along the long axis of the hippocampus during unexpectancy processing, suggesting a more uniform engagement of hippocampal circuits across the long axis during the processing of a novel experience. These results mirror previous findings shown in rodents (Penley et al., 2013). Despite the well-known differences in connectivity, anatomy, electrophysiology and gene expression along the long axis of the hippocampus (reviewed in Strange, Witter, Lein, & Moser, 2014), these three hippocampal regions increase gamma and theta power during unexpectancy processing suggesting common functional correlates of hippocampal activity along the long axis.

The power increase observed within individual sites can be driven by an increase in synaptic input to hippocampal neurons. The LFP signal not only represents synaptic inputs but also could be influenced by membrane potentials and changes of intrinsic cellular properties, (reviewed in Buzsáki, 2002; Logothetis & Wandell, 2004). In any case, to observe increases in power would require synchronized intrinsic oscillations in large number of neurons to be engaged by synaptic input. An increase in power in a certain region is also likely reflecting an increase of intrinsic activation of that region and at the same time an increase in synchrony of the input to that region. Thus, these

results reflect a numerically larger, and temporally more precise, network engaged in a common process. This mechanism can be used by the hippocampus to encode the features of novel items that can lead to an increase of subsequent retention (reviewed in Nyhus & Curran, 2010).

One of the aims of the present study was to identify modulations of the higher frequency activity during novelty processing along the long axis of the hippocampus. To address this, we used the CFC envelope method to determine modulation of the gamma frequency activity by the lower frequency ranges. Gamma oscillations typically emerge from the coordinated interaction of excitation and inhibition, which can be detected as LPFs. But also, gamma rhythm typically concurs with irregular firing of single neurons, and the network frequency of gamma oscillations varies extensively depending on the underlying mechanism (Buzsáki & Wang, 2012). There are two main models for the generation of gamma oscillations, the Inhibitory-Inhibitory (I-I) and the Excitatory-Inhibitory (E-I) neurons model. The I-I model states that gamma oscillations can emerge in two different ways: irregular or asynchronous activity of single interneurons and gamma oscillations of interneurons groups. When the input drive is relatively tonic, neurons can fire spikes with a well-defined periodicity generating a gamma oscillation (Kopell & Ermentrout, 2002). By contrast, if neurons receive stochastic inputs and fire spikes irregularly, this can also cause gamma oscillation to emerge (Ardid, Wang, Gomez-Cabrero & Compte, 2010; Brunel & Wang, 2003; Brunel, 2000; Brunel & Hakim, 1999; Economo & White, 2012; Geisler, Brunel, & Wang, 2005). Thus, the frequency of gamma oscillations in the I-I model is determined

mainly by the kinetics of the inhibitory postsynaptic potentials and the net excitation of interneurons (Buzsáki et al., 2012).

The E-I model is based on the reciprocal connections between pools of excitatory pyramidal (E) and inhibitory (I) neurons (Börgers & Kopell, 2003; Brunel & Wang, 2003; Ermentrout & Kopell, 1998; Freeman, 1975; Geisler et al., 2005; Leung, 1982; Wilson & Cowan, 1972). In this model, two-neuron pools elicit fast excitation of the pyramidal cells, with delayed feedback inhibition from interneurons producing an alternant excitation-inhibition pattern in time. With appropriate strength of excitation and inhibition, cyclic behavior may persist for a while generating a gamma oscillation (Buzsáki et al., 2012).

Interestingly a peak frequency analysis revealed that population theta frequency directly measured from the LFP signal remains stable along the long axis of the hippocampus as has been previously shown in rodents (Patel et al., 2012), being on average decreased for unexpected condition also consistent with evidence from rodents data (Jeewajee et al., 2008).

We expected to observe lower frequencies modulating fast gamma envelope with decreasing frequency range from posterior to anterior portions of the hippocampus during novelty processing. Theta organizes spiking in hippocampal pyramidal cells (Lisman & Jensen, 2013). We are not recording spikes but we use gamma as a surrogate marker of spiking activity and the envelope method was used to ascertain the oscillatory frequency of cells assemblies. We expected to observe a decrease in frequency from the tail to the body. This decrease in oscillatory frequency from dorsal (posterior) to ventral

(anterior) hippocampus has been shown in rodents. The oscillatory frequency of place cells decreases along the dorso-ventral axis, whereas the size of place fields increases (Kjelstrup et al., 2008; Maurer et al., 2005; Royer, Sirota, Patel, & Buzsáki, 2010). This decreasing oscillatory pattern could be arising from the entorhinal cortex, which is known to be the gate of sensory information for novelty processing of the hippocampus (reviewed in Lisman & Grace, 2005). Novelty has been shown to increase scale of grid cells in entorhinal cortex (Caswell, Hayman, Burgess, & Jeffery, 2007), which is associated with a decrease in oscillatory frequency from dorsal to ventral portions of the entorhinal cortex (Giocomo, Zilli, Fransén, & Hasselmo, 2007). However, we do not observe any significant difference in the frequency of the gamma envelope from posterior to anterior hippocampal portion -using gamma envelope as a surrogate of spiking activity.

Furthermore, the power increase observed in the theta band for novelty processing was concomitant to an increase in theta synchrony (coherence) along the longitudinal axis of the hippocampus which reflects synchronicity between regions (head, body and tail) involved in novelty processing. This can be interpreted as a better synchronicity to convey and receive a novel message in the theta band across the long-axis as was previously suggested in rodents (Penley et al., 2013). However, the lack of increased phase synchrony (observed with PLV measures) during novelty processing between-region, lead us to speculate that the increase in coherence observed here and in rodents (Penley et al., 2013) might be driven by the increased power observed during unexpectancy processing. Furthermore, no differences were observed when comparing synchrony between different portions along the long-axis, possibly reflecting a

consistent phase relationship. This is in line with previous studies in rodents (Patel et al., 2012) and in humans (Zhang & Jacobs, 2015) showing a theta traveling wave pattern along the long-axis of the hippocampus, which in turn motivated our next study (see Chapter 4c).

Similarly to the present study, a number of human and animal studies have demonstrated a relationship between theta power and coherence, as well as gamma and theta/gamma coupling at both medial temporal lobe and other neocortical sites in relation to information processing (Fell et al., 2001, 2003; Sederberg et al., 2003; Canolty et al., 2006; Tort et al., 2009; Shirvalkar et al., 2010; Colgin et al., 2009). The findings provided here suggest that (1) novelty processing engages the entirety of the longitudinal axis to encode novel sensory experience via theta and gamma power increases in every region (2) Novelty does not change the theta oscillatory frequency that modulates gamma as a function of the position along the longitudinal axis of the hippocampus, expected to be faster at posterior portions while (3) population theta remains stable along the long axis being decreased during novelty processing. (4) Novelty increases coherence between different regions along the long-axis of the hippocampus in the theta band, but does not increase PLVs, possibly meaning that this increase in coherence is due to an increase in the theta power observed. (5) The lack of a difference between-region iCoh and PLV observed suggest a consistent phase relationship along the long-axis of the hippocampus which motivated the next study of travelling waves (see Chapter 4c).

Chapter 4c

**Travelling waves along the long-axis of the
hippocampus**

4.1 Abstract

Travelling waves are present in different brain structures at different frequency ranges and in different species. The relationship of the phase of the traveling waves with neuronal firing or other oscillations is thought to represent a mechanism to code information by means of the expression of different phases along the same structure or between structures at the same time. These traveling waves have been shown in the theta range in the hippocampal formation of rodents, traveling along the long-axis first. Later, similar patterns were found in humans. In the present study, we confirm the existence of theta (4-8Hz) traveling waves along the long-axis of the hippocampus and go beyond previous work by providing evidence that the frequency range of the travelling waves extends to the alpha band (8-12Hz). Furthermore, the traveling wave pattern observed was not modulated by presentation of unexpected stimuli.

4.2 Introduction

Traveling waves have been observed in different brain regions and at different frequency bands, indicating that parts of the same structure can experience different phases of a certain oscillation that could serve as a spatial-phase coding mechanism. For instance, it has been suggested that travelling waves in visual cortex at alpha frequency might serve to leave parts of the visual field unresponsive by preventing gamma band synchronization. It has been suggested that such traveling waves can create sweeps scanning the visual field to tag visual features to different phases of the oscillations (Ermentrout & Kleinfeld, 2001). There is also evidence showing bursts of gamma activity propagating over neocortex. These propagating gamma bursts are locked to the phase of traveling alpha waves, suggesting that alpha oscillations serve to coordinate gamma activity not only in time, but also in space (Bahramisharif et al., 2013).

Moreover, work in rodents (Lubenov & Siapas, 2009; Patel et al., 2012) and in humans (Zhang & Jacobs, 2015) showed a theta traveling wave pattern from the posterior to the anterior hippocampal formation (dorsal to ventral in rodents). These findings suggest that there are different phases in different parts of the hippocampal formation, which might represent a mechanism to code information.

Lubenov and Siapas observed a systematic advance of theta phase in the dorsal hippocampus of rodents and hypothesized a full cycle (~360 degrees) phase shift from septal to temporal poles. They concluded that this could imply that outputs from the two poles of the hippocampus would affect their joint targets in a temporally synchronous manner, while the intermediate parts would remain temporally segregated from either

pole (Lubenov & Siapas, 2009). Subsequently, Patel and colleagues showed a monotonic theta phase shift with distance along the longitudinal axis, reaching ~180 degrees between the septal and temporal poles (Patel et al., 2012). They explain this discrepancy with the use of different axes of phase measurements compared to Lubenov & Siapas (2009). That is Lubenov et al. computed the phase combining anteroposterior and mediolateral propagation of theta waves in the dorsal hippocampus. Given that theta waves travel not only along the long-axis but also in the CA1-CA3 direction, phase shifts in both septotemporal and CA3-subicular axis could have resulted in overestimation of the phase advancement along the long-axis.

Travelling waves have been also observed in human hippocampus (Zhang & Jacobs, 2015), measured at a broader range of frequencies compared with rodents suggesting that traveling theta oscillations are important functionally across species because they coordinate phase coding throughout the hippocampus in a consistent manner.

Hippocampal theta activity has been related to many aspects of cognition (Colgin, 2016), including memory and spatial navigation (Landfield, McGaugh, & Tusa, 1972; Seager, Johnson, Chabot, Asaka, & Berry, 2002; Winson & Abzug, 1978). Theta has been also shown to increase amplitude during hippocampal dependent behaviors (Vanderwolf, 1969), to modulate synaptic plasticity (Huerta & Lisman, 1995; Larson et al., 1986; Pavlides et al., 1988) and to coordinate neural networks (Buzsáki, 1996; Miller, 2013; Siapas, Lubenov, & Wilson, 2005; Sirota et al., 2008). A dominant view of the role of hippocampal theta phase is to indicate the transition between processing states –e.g., encoding and retrieval– (Hasselmo, Bodelón, & Wyble, 2002; Miller, 2013;

Pavlidis et al., 1988; Stewart & Fox, 1990). The observation of travelling theta waves, however, requires that the functional role of theta to be updated. For example, different theta phases at different locations along the long-axis of the hippocampus raises the possibility that the theta phase can be signalling future and past events, with different phases at different positions within the hippocampus representing information about events at different times.

In the present study we directly recorded from the hippocampal in patients implanted with intracranial electrodes for pre-surgical evaluation of epilepsy, while performing an oddball task (previously presented in Axmacher et al., 2010). We used contacts along the long-axis of the hippocampus (see Chapter 4a) to explore traveling wave patterns along the long-axis of the hippocampus.

We hypothesized here that theta is travelling along the long-axis from posterior to anterior segments of the hippocampus as has been previously shown. In addition we will refine the specificity of the traveling wave by partitioning the broadband theta reported in (Zhang & Jacobs, 2015) into theta and alpha bands. Previous study (Zhang & Jacobs, 2015) has shown that the traveling pattern is not modulated by working memory. Given a critical hippocampal role in novelty detection (see Chapter 4a) we also examined novelty dependent changes in traveling waves.

4.3 Methods

As recently suggested, theta is traveling along the long-axis of the hippocampus in humans (Zhang & Jacobs, 2015) and rodents (Patel et al., 2012). As previously described (see Chapter 4a), we re-referenced our data to an average reference of all hippocampal contacts, similar to other studies (Alexander, Jurica, Trengove, & Nikolaev, 2013; Bahramisharif et al., 2013; Massimini, Huber, Ferrarelli, & Hill, 2004; Meij, Kahana, & Maris, 2012; Munck, Goncalves, Huijboom, & Kuijer, 2007; Patten, Rennie, Robinson, & Gong, 2012; Zhang & Jacobs, 2015). One of the reasons for this is to have a reasonable amount of contacts along an axis. Furthermore, this kind of montage reportedly yields larger theta signals (Zhang & Jacobs, 2015).

From our pool of 11 patients, we included 5 patients with consecutive electrodes along the long-axis of the hippocampus and calculated traveling waves for delta (1.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz) and beta (13- 30 Hz) bands to explore the frequency specificity of these travelling waves. An online filter of 0.1 Hz was used and signal was not detrended in order to allow delta band exploration. We used custom scripts running in Matlab. Trials were defined from -0.1 to 2 s peri-event onset and differentiated into expected and unexpected conditions. Next, we band pass filtered the data in the band of interest using a plateau shaped band-pass filter with 15 transition zones. We chose the most anterior hippocampal contact as a reference channel and extracted 1s segments of the filtered data locked to the peaks of the reference channel (500ms before and after the peaks of the reference channel) and averaged the extracted data per trial and per contact.

The resulting band pass filtered signal locked to the reference channel was visually inspected looking for traveling wave pattern.

Next, we used a different approach to calculate traveling waves. In this approach, we first filtered the signal with the same filter introduced before, then we calculated the instantaneous phase via the angle of the Hilbert transform for each trial and contact. Using the circular statistics toolbox CircStat2012a (<https://es.mathworks.com/matlabcentral/fileexchange/10676-circular-statistics-toolbox-directional-statistics->) (Fisher, 1993) we calculated the circular mean of the phases across trials and the circular distance between each channel and the reference channel - the most anterior- for every trial. We then plotted an angle histogram of the phase distance per channel and conditions for all the trials at an arbitrary time point (t=100ms). A non-uniform distribution of the phase shift between each channel and the reference channel was tested using a Rayleigh test to assess phase locking across trials corrected for the number of contacts. The mean resultant vector length was calculated for the distance between the phase of each contact and the reference channel. We randomly selected the number of trials for the expected condition to match the number of unexpected trials and averaged across 1000 randomizations.

4.4 Results

We explored travelling waves along the longitudinal axis of the hippocampus for the theta, but also for the alpha, beta and delta band to determine if this traveling waves are selective in frequency. We observed the theta peaks of the LFP signals -locked to the most anterior contact as a reference- advancing in time from posterior to anterior contacts along the long-axis of the hippocampus. This pattern was observed for two out of five patients in the theta band (4-8Hz) (Figure 33) and for four out of five patients in the alpha band (8-13Hz) (Figure 34). Representative patients were selected to show the non-travelling wave pattern in the delta (1.5-4Hz) (Figure 35) and beta (13-30Hz) (Figure 36) bands. Note that the trials were filtered in a certain frequency band of interest and for that reason less amplitude is observed at both sides of the averaged trials and also that 500ms represents the middle time point of the resultant 1s extracted signals (see 4.3 Methods). Therefore, for the theta, alpha and beta bands 200 ms were depicted around middle time point and 500ms for the delta band.

Figure 33. Theta travelling waves. Two patients with theta traveling waves across neighbouring electrodes. Displayed filtered signals from 4 to 8Hz locked to the peaks of the most anterior hippocampal electrode and averaged across trials for expected and unexpected conditions.

Figure 34. Alpha travelling waves. Two patients with alpha traveling waves across neighbouring electrodes. Displayed filtered signals from 8 to 13Hz locked to the peaks of the most anterior hippocampal electrode and averaged across trials for expected and unexpected conditions

Figure 35. Non-traveling pattern in Delta band. Four representative patients. Displayed filtered signals from 1.5 to 4 Hz locked to the peaks of the most anterior hippocampal electrode and averaged across trials for expected and unexpected conditions.

Figure 36. Non-traveling pattern in Beta band. Four representative patients. Displayed filtered signals from 13 to 30 Hz locked to the peaks of the most anterior hippocampal electrode and averaged across trials for expected and unexpected conditions.

In our next analysis, advancing pattern in time was assessed by inspecting the instantaneous phase in every contact. In the 2 and 4 patients showing theta and alpha travelling wave respectively, we observe advancing pattern of the mean phase resultant vector for the phase distance between each channel and the most anterior channel across trials at an arbitrary time point is seen for the theta (Figure 37) and alpha (Figure 38) bands. Rayleigh test revealed the phase distance between each channel and the reference

channel to be different from the uniform distribution for the majority of the contacts for the theta band (Table 14, Table 15) and for the alpha band (Table 16, Table 17, Table 18, Table 19).

Figure 37. Polar histogram across trials for the theta phase difference between the most anterior electrode as a reference channel and each electrode along the longitudinal axis of the hippocampus for expected and unexpected conditions.

Channel		HH2-HH1	HB1-HH1	HB2-HH1	HT1-HH1	HT2-HH1	HT3-HH1	HT4-HH1
Exp	p	2.51e-23	1.01e-06	1.431e-17	1.64e-08	0.0004	2.14e-10	2.52e-07
	z	49.55	13.65	37.42	17.65	7.73	21.83	15.00
Unexp	p	2.41e-10	0.46	0.011	0.003	0.083	0.108	0.0004
	z	19.82	0.78	4.41	5.59	2.47	2.21	7.57

Table 14. Patient 43. Rayleigh test of the circular distance between the theta phase of each channel and the reference channel (most anterior) for expected and unexpected conditions. Note that significance level corrected by the number of comparisons (number of channels -1) would be 0.0071.

Channel		HH2-HH1	HB1-HH1	HB2-HH1	HT1-HH1	HT2-HH1
Exp	p	2.43e-15	9.02e-34	7.53e-50	1.27e-73	5.84e-12
	z	32.82	71.71	103.35	146.23	25.39
Unexp	p	0.001	0.0004	1.447e-07	1.51e-14	0.062
	z	6.83	7.75	15.01	28.57	2.77

Table 15. Patient 62. Rayleigh test of the circular distance between the theta phase of each channel and the reference channel (most anterior) for expected and unexpected conditions. Note that significance level corrected by the number of comparisons (number of channels -1) would be 0.01.

Figure 38. Polar histogram across trials for the alpha phase difference between the most anterior electrode as a reference channel and each electrode along the longitudinal axis of the hippocampus for expected and unexpected conditions.

Channel		HH2-HH1	HB1-HH1	HB2-HH1	HT1-HH1	HT2-HH1	HT3-HH1	HT4-HH1
Exp	p	1.54e-25	0.027	3.77e-08	2.10e-10	2.99e-07	5.91e-19	9.83e-12
	z	54.13	3.62	16.84	21.85	14.83	40.37	24.78
Unexp	p	6.32e-06	0.096	0.0003	0,010	0.053	0.016	0.595
	z	11.35	2.33	7.93	4.50	2.91	4.07	0.52

Table 16. Patient 43. Rayleigh test of the circular distance between the alpha phase of each channel and the reference channel (most anterior) for expected and unexpected conditions. Note that significance level corrected by the number of comparisons (number of channels -1) would be 0.0071.

Channel		HH2-HH1	HH3-HH1	HB1-HH1	HB2-HH1	HB3-HH1	HT1-HH1	HT2-HH1
Exp	p	1.29e-39	3.15e-28	7.13e-09	0.007	1.25e-05	2.46e-40	1.57e-27
	z	85.72	61.43	18.60	4.98	11.23	87.24	59.92
Unexp	p	1.49e-08	1.85e-07	0.0003	0.019	0.052	8.69e-05	0.036
	z	17.34	15.01	7.90	3.90	2.94	9.19	3.31

Table 17. Patient 45. Rayleigh test of the circular distance between the alpha phase of each channel and the reference channel (most anterior) for expected and unexpected conditions. Note that significance level corrected by the number of comparisons (number of channels -1) would be 0.0071.

Channel		HH2-HH1	HB1-HH1	HB2-HH1	HT1-HH1	HT2-HH1
Exp	p	6.39e-14	1.56e-27	1.35e-36	5.00e-59	2.96e-10
	z	29.71	58.85	77.42	120.45	21,59
Unexp	p	0.022	8.88e-05	3.06e-07	7.14e-16	0.0005
	z	3.78	9.09	14.33	30.94	7.43

Table 18. Patient 62. Rayleigh test of the circular distance between the alpha phase of each channel and the reference channel (most anterior) for expected and unexpected conditions. Note that significance level corrected by the number of comparisons (number of channels -1) would be 0.01.

Channel		HH2-HH1	HH3-HH1	HB1-HH1	HB2-HH1	HT1-HH1	HT2-HH1
Exp	p	2.09e-127	4.319e-07	2.44e-05	8.41e-23	2.54e-67	1.00e-57
	z	245.67	14.55	10.57	49.48	140.69	122.00
Unexp	p	3.79e-35	0.002	0.65	1.33e-09	1.01e-19	2.30e-17
	z	63.95	6.18	0.44	19.49	39.17	34.83

Table 19. Patient 71. Rayleigh test of the circular distance between the alpha phase of each channel and the reference channel (most anterior) for expected and unexpected conditions. Note that significance level corrected by the number of comparisons (number of channels -1) would be 0.0083.

Please note that Rayleigh test can be biased by the number of trials so lower p values can be observed for Expected condition. We further tested for a difference between conditions for the mean resultant vector of the distance between each contact and the reference channel. The result for the Wilcoxon test did not revealed significant difference between expected and unexpected conditions (Table 20).

Wilcoxon (Z, p)	Theta	Alpha
Patient 43	Z = 53; p < 1	Z = 49 ; p < 0.71
Patient 45	-	Z = 50 ; p < 0.80
Patient 62	Z = 23; p < 0.42	Z = 27; p < 1
Patient 71	-	Z = 42 ; p < 0.7

Table 20. Wilcoxon test comparing expected and unexpected mean resultant vector length of the distance between the phase of each contact and the reference channel.

4.5 Discussion

The present study explored travelling waves along the longitudinal axis of the hippocampus for the theta, but also for the alpha, beta and delta band to test the frequency specificity of the traveling wave pattern. The results showed that there is a traveling wave from posterior to anterior hippocampus specific for the theta (4-8Hz) and for the alpha band (8-13Hz) regardless of novelty processing –the pattern is present for expected and unexpected conditions. We furthermore explore the traveling waves for the delta and beta bands and no traveling wave patterns were observed suggesting this phenomenon to be specific for theta and alpha bands.

The fact that we observed theta travelling waves along the long-axis of the hippocampus is in line with previous findings in rodents (Lubenov & Siapas, 2009; Patel et al., 2012) and with more recently results observed in humans (Zhang & Jacobs, 2015).

The classical model for hippocampal theta generation postulates that the medial septum diagonal band of Broca (MS-DBB) is a rhythm generator (pace-maker), which supplies phasic modulation to the hippocampus. This is based on studies showing that lesioning or inactivation of MS-DBB neurons, abolishes theta waves in cortical targets (Petsche et al., 1962). This classical model assumes that all pyramidal cells receive coherent excitatory input-via the perforant path- and inhibitory input –from the septum- to feedforward inhibitory neurons. However, this model is based on the assumption that the mutual connections between MS-DBB and the hippocampus/entorhinal cortex are such that the septum is the pace-maker and the hippocampus is the follower which is potentially an over simplification. However, there is evidence that indicates that the

recurrent circuit of the CA3 region may function as an intrahippocampal theta oscillator (Bragin et al., 1995). Theta dipoles, which remain after removing the entorhinal inputs, can be accounted for by the more proximal dendritic excitation of CA1 pyramidal cells by the associational (Schaffer) collaterals (Kocsis et al., 1999). Such lesions render the remaining theta oscillation atropine sensitive (Buzsáki, & Vanderwolf, 1983). This idea of atropine-sensitive form of theta, typically from 4 to 7 Hz result from excitation of the cholinergic fibers, comes from observation that muscarinic blockers, such as atropine, completely eliminate theta oscillations in anesthetized animals (Kramis, Vanderwolf, & Bland, 1975). This suggests that the atropine-sensitive form of theta emerges in the CA3 recurrent collateral system (Kamondi, Acsády, Wang, & Buzsáki, 1998; Kocsis et al., 1999). This idea is also supported by in vitro studies where slices of the CA3 region can generate theta oscillations (Konopacki et al., 1987). By contrast, extracellular field recordings in the intact isolated hippocampus in vitro show that atropine-resistant theta generators in CA1 were organized along the septotemporal axis and arose independently from CA3 (Goutagny et al., 2009). In summary, an alternative model (see Buzsáki, 2002 for review) suggests that the extracellular currents underlying theta waves are generated not only by the entorhinal input, but also CA3 (Schaffer) collaterals, and pyramidal cell dendrites.

The existence of a theta traveling wave along the long-axis of the hippocampus means that different phases of the theta signal are occurring simultaneously at different locations. This could imply that traveling waves serve to label simultaneously perceived features in the stimulus stream with a unique phase. There are examples in the spatial navigation literature reporting phase coding in the hippocampus for facilitating

encoding of behaviorally relevant information. An impressive example of this phenomenon are place cells, which use the theta phase to represent the spatial location of the animal (O'Keefe & Recce, 1993; Jensen & Lisman, 2000; Huxter et al., 2003). In the same manner, other studies have reported this theta phase coding to signal the timing of events (Jensen and Lisman, 1996;Dragoi & Buzsaki, 2006; Lubenov & Siapas, 2009). The hypothesis of theta phase representing time and space, together with the fact that the theta phase is progressing along the long-axis of the hippocampus could imply that individual neurons are coding future, present and past events and locations, by each individual cell spiking at separate local theta phase. Interestingly, these traveling waves are progressing from posterior to anterior hippocampal contacts. If the dorsal to ventral increase in place field size observed in rodents (Kjelstrup et al., 2008) is evident in humans, this progressing would be associated. This would imply that posterior hippocampal neurons fire earlier, representing accurate locations, followed by later activation of anterior place cells, representing coarser spatial information. Furthermore, there is dominant view of the role of hippocampal theta phase is to indicate the transition between processing states –e.g., encoding and retrieval- (Hasselmo et al., 2002; Miller, 2013; Pavlides et al., 1988; Stewart & Fox, 1990). Thus, if encoding is more likely to occur at the peak of the theta signal and retrieval at the trough (Hasselmo et al., 2002) and if the place field size increases from posterior to anterior hippocampus in humans, the existence of a theta traveling wave suggests that while the tail is experiencing a peak (representing small place field size –details- and encoding state) the head is experiencing a trough (representing big place field size – context- and retrieval state) and vice versa. This suggests that the hippocampus puts details into context and contextualizes details every ~200ms.

The observation of theta travelling waves along the long-axis of the hippocampus can also provide insight about the oscillators generating this phase lag of the theta rhythm along the long-axis. The simplest mechanism explaining this phenomenon would be a single oscillator (SO) generating this rhythm (“septal theta pace-maker”) (Stumpf, Petsche, & Gogolak, 1962) and the delays observed due to the propagation velocity of septo-hippocampal afferents. However, this model requires precise tuned delays between septal afferents to different regions of the hippocampus and they would also have to match entorhinal inputs. These conduction delays would need to be fixed, implying that wave propagation speeds would be constant regardless of frequency. Contrarily, Zhang & Jacobs (2015) found the wave propagation speeds to be frequency-dependent rather than constant. The conduction velocities of thickly myelinated septo-hippocampal GABAergic neurons (Freund & Antal, 1988), which according to the classical model set theta frequency rhythms in the hippocampus (Lee et al., 1994; Yoder & Pang, 2005), are an order of magnitude faster than the propagation velocity of theta waves. This also challenges the SO model. Moreover, different septotemporal segments of the hippocampus are not innervated by axons of the same septal neurons (Gage et al., 1983). Furthermore, phase lags between different hippocampal contacts indicate that individual neurons can maintain synchrony with cells at other positions along the length of the hippocampus while experiencing only its local theta phase. SO models of traveling waves cannot give rise spatial phase patterns, because they do not provide a consistent spatial phase distribution across different frequencies. By contrast, coupled oscillators could provide this mechanism based on the synchronous activation of assemblies of neurons.

Oscillating neurons are described by a system of non-linear differential equations with a stable limit cycle –e.g., isolated neuron current is moving $I_1 < I < I_2$, where I is the external current injected into the neuron, with period T -. The coupling appears as an additional term in the evolution equations for the membrane potentials of the neurons. In weakly coupled oscillators the phase dynamics of the oscillators are completely defined by an effective interaction that can be evaluated in terms of the original system and describes the slowing-down or acceleration of the phase due to the interaction between oscillators. This approach is valid as long as the shape of the limit cycle is only weakly altered by the interaction; this does not entail that effects on the phase are small (Hansel, Mato, & Meunier, 1993).

Together, this suggests that a weakly coupled intrahippocampal-entorhinal matched oscillators model can be a feasible mechanism for theta travelling waves (Kopell, & Ermentrout, 1986) (Figure 39). A possible intra-hippocampal generator can be CA3 as previously suggested by Patel et al (2012) given that both the CA3 recurrent system and in vitro slices of the CA3 region can generate theta oscillations (Kocsis et al., 1999; Konopacki et al., 1987). In addition, delays with similar magnitudes as documented in (Patel et al., 2012) have been reported in the isolated CA3 region in vitro (Miles et al., 1988).

Figure 39. Schematic of the travelling waves along the long-axis of the hippocampus. a) A schematic showing a view of the hippocampus with the dentate gyrus (DG) visible inside with an electrode array along the long axis. The main hippocampus body as well as the uncus and landmark used to define HH end (uncal apex) are indicated. In green the hypothesized CA3-Entorhinal matched weakly coupled oscillators generating theta travelling waves from posterior to anterior hippocampus. In blue theta waves in different contacts with red dots showing the progression of the theta phase. b)–e) Coronal slices showing the hippocampal subfields in the anterior hippocampus. From a) to e) modified from (Zeidman & Maguire, 2016).

The fact that we did not see a modulation of the travelling wave patterns by novelty processing suggests that hippocampal activity exhibits analogous anterior to posterior phase differences regardless of unexpectedness and therefore indicate that this traveling waves are not coding unexpectedness. This is consistent with results presented in Chapter 4b, showing there was no difference in the inter-region PLVs between expected and

unexpected conditions. Thus, unexpectancy processing is not disrupting the phase consistency observed along the long axis. This lack of correlation with behavior was also observed in (Zhang & Jacobs, 2015), where they did not observe any differences in the travelling wave pattern between conditions in a working memory task.

We furthermore observe frequencies in the alpha range traveling along the long-axis from posterior to anterior parts of the hippocampus. The frequency range used in the only study in humans that theta travelling waves have been shown (Zhang & Jacobs, 2015), was theta band from 2-10 Hz which is rather broad compared to conventional definitions. This frequency band might therefore also include activity around 10 Hz, which is commonly considered to be the alpha band at least in scalp recorded EEG. Indeed, Zhang & Jacobs (2015) show an alpha peak in the power spectrum, which is, in some cases, even higher than the theta peak, revealing a strong presence of alpha power. In the present study, we used a more fine grained analysis, including the traditional convention in humans for different frequency ranges, defining delta from 1.5 to 4 Hz; theta from 4 to 8 Hz; alpha from 8 to 13 Hz and beta from 13 to 30 Hz. Given our results showing that not only theta but also alpha is travelling –a pattern observed even in more patients for the alpha compared to the theta band- it is possible that there is a common oscillator for both low frequency bands. Thus, we conclude that lower frequency ranges that include theta and alpha bands are traveling along the long-axis of the hippocampus from posterior to anterior portions.

Remains a question if this travelling pattern observed in theta and alpha bands is broadband or if, by contrast, is bimodal being theta and alpha oscillations travelling

separately. A possible way to disentangle this would be to compute each contact's power spectrum and identify electrodes with narrowband oscillations visible above the $1/f$ background power spectrum and custom each band width for each peak observed in each subject.

In (Zhang & Jacobs, 2015) performing extensive preprocessing to determine a traveling wave pattern including clustering of successive contacts, contact exclusion if they were not phase locked to the average phase of the cluster. Following this procedure for the 14 patients they ended up with 6 out of 11 clusters showing the traveling pattern. It appears therefore that detection of a traveling wave pattern, at least with the methods showed here and in (Zhang & Jacobs, 2015) it is not possible in all patients. To better understand this traveling wave pattern observed, and the fact we did not observed this pattern for every patient similarly to previous study, further analysis would be necessary. A possibility would be extracting for each trial a measure of “travelness degree” instead of averaging the bandpass filtered signals. This can be done either testing for a relationship between the electrode location and the phase difference from the reference, or testing for a relationship between the electrode location and the time lags between theta peaks of each contact and the reference. It is possible to generate a shuffled distribution of the phase distance between each contact from the reference channel by randomly permuting the location of the electrodes. Then for both real data and shuffled data a regression model can be used to fit the relative phases and the position of the electrodes. Statistical significance of the “travelness degree” can be estimated by comparing the result of the regression for both real and shuffled data. Given that the CO model predicts a correlation between temporal frequency and

propagation speed while the SO model predicts no such relation, will be also interesting to look at the relationship between temporal frequency and propagation speed and spatial wavelength as in (Zhang & Jacobs, 2015) to compare how different waves propagated and distinguish the model that best explains these waves' propagation.

Chapter 5

Conclusions

The experiments presented in this thesis used different techniques –behavioral, fMRI, pupillometry and intracranial recordings- to better understand mechanisms underlying memory enhancement in humans. Two main factors that modulate episodic memory in humans have been the focus of this research: voluntary movements and novelty. This thesis presents five major findings. First is the demonstration of a noradrenergic mechanism mediating an episodic memory encoding enhancement by taking action. Secondly anterior, middle and posterior parts of the hippocampus exhibit common oscillatory response properties across the long-axis. We suggested here a possible source of LFP evoked responses between the HH and HB segments within the anterior hippocampus. Thirdly, an evaluation of oscillatory properties in the theta and gamma bands provided evidence that the theta population frequency remains constant along the long-axis decreasing with novelty processing while the theta oscillatory frequency coupled to gamma is not changing from posterior to anterior segments of the hippocampus. Fourthly, a between-region coherence in the theta band and within-region power increase in the theta and gamma bands during novelty processing was observed along the long axis of the hippocampus. However, phase locking across and within portion was not affected by expectancy. Finally, the results in this thesis confirm a theta travelling wave along the long axis of the hippocampus from posterior to anterior regions, and furthermore uncovered a traveling wave in the alpha band. This potentially represent a phase code along the long-axis of the hippocampus to encode information.

5.1 Voluntary movements enhances episodic memory via a noradrenergic mechanism

The conclusion from Chapter 3 in this thesis is that taking action enhances episodic memory encoding via a noradrenergic engagement. Over a series of behavioural experiments we observed an action-induced episodic memory enhancement. Converging evidence from fMRI and pupilometry measures -an indirect index of LC activation (Alnaes et al., 2014; Gilzenrat, Cohen, Rajkowski, & Aston-Jones, 2003; Gilzenrat et al., 2010; Jepma & Nieuwenhuis, 2011; Joshi et al., 2016; Murphy et al., 2014, 2011b; Rajkowski, Kubiak, & Aston-Jones, 1993)- demonstrate a noradrenergic drive in the episodic memory enhancement observed during voluntary movement execution. Furthermore, this LC activation is functionally coupled with a memory target area, parahippocampal gyrus, suggesting a framework in which noradrenaline release triggered by voluntary movements engages memory target areas to promote episodic memory encoding. We further assessed the noradrenergic role in the action-induced memory enhancement, showing that this is also modulated by emotional arousal given the established role of the noradrenergic system in memory consolidation for emotional stimuli. Particularly, action and emotional noradrenergic drive interacts with memory performance in a way which adheres to Yerkes-Dobson law.

This thesis also provide results arguing against an inhibition induced memory impairment as other studies previously suggested to be the explanation of the behavioral effect observed (see Chiu & Egner, 2014, 2015). This was assessed by showing that, as the “inhibitory load” increased there was an increase in commission errors (Durstun et

al., 2002; Thomas et al., 2009). However, a memory disruption was not observed. Further support to discard the alternative explanation (i.e., inhibition-induced memory impairment) is given by behavioral data suggesting that this effect does not depend on the stimuli encoding time window coinciding with the established inhibition related neuronal response time window “N2” (Falkenstein et al., 1999; Gonzalez-Rosa et al., 2013; Kiefer, Marzinzik, Weisbrod, Scherg & Spitzer, 1998). Results in this thesis also provide evidence that voluntary movement-evoked memory enhancement it is observed regardless of reward anticipation. This may reflect that reward anticipation (and putative dopaminergic activity) is not required to observe an action-induced memory enhancement as has been previously suggested (Koster et al., 2015).

Therefore, this thesis suggests that voluntary movements engage LC activation with the subsequent release of noradrenaline that targets memory areas-e.g., parahippocampal gyrus- to promote memory encoding. This is in line, on the one hand with studies in monkeys showing LC activation is aligned to voluntary movements (Bouret & Richmond, 2009; Bouret & Richmond, 2015; Clayton et al., 2004; Kalwani et al., 2014; Varazzani et al., 2015), and on the other hand with the known role of NE promoting memory formation (Mcgaugh & Roozendaal, 2009; Tully et al., 2010). Results in this thesis together with emerging evidence suggesting LC loss represents a turning point in dementia in Parkinson’s and Alzheimer’s diseases progression (Braak et al., 2011; Mravec et al., 2014; Rommelfanger & Weinshenker, 2007), suggest that NE can potentially play an important role in pharmacotherapies used for the treatment of movement and memory disorder. By extension, voluntary movements during memory encoding can serve as a potential rehabilitation strategy in early stages of cognitive

impairment in dementia. However, future memory research will be needed to further understand the underlying electrophysiological mechanisms and, moreover, that Go-induced memory enhancement is observed in the elderly.

5.2 Intracranial EEG correlates of unexpectedness along the long axis of the human hippocampus

Chapter 4 in this thesis showed that not only the anterior hippocampus, as has been suggested by fMRI studies, but the entire hippocampus including middle and posterior parts are engaged in novelty detection. Thus we observe a common oscillatory response properties of different hippocampal segments despite anatomical, functional and genetic differences between different regions (reviewed in Strange, Witter, Lein & Moser, 2014).

Interestingly, a polarity inversion of the ERP observed in Chapter 4a suggests a possible electrical source of unexpected-evoked activity between hippocampal head and body that can be located within the anterior portion of the hippocampus, as it has been previously suggested (Ludowig et al., 2010). The large potential observed posteriorly might arise from parahippocampal gyrus. However, further analysis to localize these possible sources would be need.

Furthermore, an increase in power in the theta and gamma bands was observed during novelty processing in all three segments. The overall pattern replicated previously findings in humans with the same data and overlapping patients, which did not examine long-axis differences (Axmacher et al., 2010). The increase in theta power was concomitant with an increase in theta coherence between different regions along the long axis of the hippocampus possibly reflecting that different regions of the hippocampus are better synchronized to convey and receive a novelty message as has

been previously suggested in rodents (Penley et al., 2013). However, the increase in coherence was not concomitant with an increase in phase locking value, suggesting that the increase in coherence observed in this thesis in humans (and previously in rodents (Penley et al., 2013)) might be driven by amplitude differences in the theta band during unexpectancy processing. Furthermore, no differences on the synchronicity measures were observed between region comparison (head-body, head-tail and body-tail). The theta phase consistency across the long axis for both conditions, led us to explore the existence of a travelling wave along the long-axis previously observed in rodents (Lubenov & Siapas, 2009; Patel et al., 2012) and in humans (Zhang & Jacobs, 2015). Interestingly, this thesis presents a travelling oscillatory pattern from posterior to anterior portions of the hippocampus not only for theta, but also for the alpha band. Importantly, the travelling waves were not modulated by novelty processing. This is in line with results presented in this thesis showing no modulation of inter-region PLVs by unexpectancy processing. In the present study, we used a more fine grained frequency analysis, used frequently in humans for different frequency ranges, defining delta from 1.5 to 4 Hz; theta from 4 to 8 Hz; alpha from 8 to 13 Hz and beta from 13 to 30 Hz. We did not observed the traveling pattern for delta and beta bands. Thus, we conclude that lower frequency ranges that include theta and alpha bands are traveling along the long-axis of the human hippocampus from posterior to anterior portions. These findings help to better compare models of possible oscillatory generators within the hippocampus. However, further analysis will be necessary to better understand the features of the traveling wave pattern in the theta and alpha ranges (broadband or bimodal?), and to explain why the pattern it is not observed in every patient. A potential interpretation of the existence of theta travelling waves from posterior to anterior portions of the

hippocampus, could imply that posterior hippocampal neurons fire earlier, representing accurate locations, followed by later activation of anterior place cells representing coarser spatial information. Assuming findings in rodents showing increased place field size from posterior to anterior hippocampus (Kjelstrup et al., 2008) extends to humans, and that encoding is more likely to occur at the theta peak while retrieval at the trough (Hasselmo et al., 2002), another feasible functional explanation for the theta traveling waves is to be contextualizing details and putting details into context every 200ms.

Finally, a peak frequency analysis revealed that population theta frequency directly measured from the LFP signal remains stable along the long axis of the hippocampus as has been previously shown in rodents (Patel et al., 2012). The peak frequency slightly decreased on average for the unexpected condition, also consistent with evidence from rodents data (Jeewajee et al., 2008). Furthermore, we did not observed lower frequencies modulating the gamma envelope, as we expected, with decreasing frequency range from posterior to anterior segments of the hippocampus during novelty processing.

The results presented in this thesis give further insight on the understanding of neural oscillatory mechanism underlying during novelty processing in the human hippocampus, which remains currently largely unexplored.

In summary, using a multimodal approach, several mechanisms important for the upregulation of episodic memory in humans have been identified in this thesis

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