Brain oscillations and novelty processing in human spatial memory

Raphael Samuel Matthew Kaplan

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Supervisor: Neil Burgess

Declaration:

I, Raphael Samuel Matthew Kaplan, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:

Date:

Abstract:

Hippocampal activity in rodent model systems is commonly associated with movement and exploratory behaviour, while human hippocampal research has traditionally focused on mnemonic function. I attempted to bridge this gap with a set of experiments where human participants performed an interactive virtual navigation paradigm that resembled rodent spatial exploration tasks, in conjunction with neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG). I then used this interactive paradigm to examine the oscillatory correlates of memory, novelty and the behavioural relevance of the default mode network.

The first experiment used MEG and fMRI to examine whether the movement-related theta rhythm (4-8 Hz) recorded from the rodent hippocampus has a measurable human analog. I found that the human hippocampal theta rhythm supports memory, and may coordinate exploratory movements in the service of self-directed learning. In further analyses in Experiment 2, during cued spatial memory retrieval, I observed that medial prefrontal cortex theta phase couples with ongoing theta oscillations in the right anterior medial temporal lobe and with neocortical gamma (65-85 Hz) amplitude.

In Experiment 3, with fMRI I investigated the effect of environmental novelty versus object novelty during the navigation task and found that hippocampal activity is modulated only by environmental novelty, while the fusiform gyrus/posterior parahippocampal cortex responded to object novelty. Finally, in Experiment 4 using 3T and high-field 7T fMRI, I investigated endogenous (task-free) periods that flanked different stages of a spatial navigation paradigm to determine how endogenous slow oscillations in the default mode network correlate with subsequent

spatial memory performance and found mixed evidence that default mode network activity predicts individual performance.

Finally, I discuss my results in the context of recent findings in spatial memory and novelty processing, and consider the relationship between the human hippocampus and rodent model systems.

Dedication

To friends and family

Acknowledgements

Writing a thesis can be a difficult task, but it has almost been an enjoyable process, because of the generous tutelage and assistance I've received from others.

I want to first thank my primary supervisor at UCL, Neil Burgess and supervisor at NIH, Peter Bandettini. Neil has easily been the best teacher I have ever had and Peter has opened so many different opportunities for me, ones that I could have scarcely imagined when first learning about cognitive neuroscience.

Furthermore, I would like to thank Jonathan Roiser and Barry Kaplan along with Margarita Valencia for putting in the necessary legwork to have me as the pilot student for a joint neuroscience PhD program between the NIH and UCL. I could never have had a comparable experience anywhere else.

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Final thanks are reserved for my parents, whose steady guidance and unwavering support have given me the wherewithal to adjust to every challenge thrown my way.

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Chapter 1

Introduction to Memory & Cognitive Maps

1.1 Preface

I am dividing my research between laboratories at the UCL Institute of Cognitive Neuroscience and the National Institute of Mental Health (NIMH) for a joint PhD in neuroscience. The supervisors of my collaborative PhD are Neil Burgess, a spatial cognition and memory researcher at UCL and Peter Bandettini, a neuroimaging methods researcher at the NIMH. Broadly speaking, the primary focus of my thesis is to use neuroimaging approaches, namely functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG), to investigate oscillatory activity in brain networks associated with spatial navigation and episodic memory.

Learning and memory-related behaviours function on different time scales, and one way to investigate their neural correlates is by measuring oscillatory activity during cognitive tasks. A wide range of animal models of learning and spatial exploration, particularly in rodents, have observed behaviourally relevant oscillatory activity from the level of single cells to neural systems. Furthermore, recent methodological advances in non-invasive neuroimaging techniques allow memory researchers to examine oscillatory activity measured by magnetoencephalography (MEG) and fluctuations in the functional magnetic resonance imaging (fMRI) signal. Whether it is slow 0.01-0.1 Hz fluctuations measured by the blood-oxygen-level-dependent (BOLD) signal with fMRI or fast 30-100 Hz gamma oscillations measured with MEG, there are many potential cognitive implications for neural oscillatory activity. By using these techniques, we can determine the functional connectivity of brain networks at different time scales, which in turn could potentially unlock further insights into learning and memory.

1.2 Cognitive maps and the hippocampus

For well over a century, since the times of Hermann von Helmholtz and William James, we have had the idea that the brain is a dynamic series of interacting networks that change based on task and metabolic demands. The plasticity of these networks allows for adaptive behaviour and a critical nexus for this type of cognitive flexibility is the hippocampus. The hippocampus has a unique laminar structure that may contribute to the generation of characteristic oscillatory fields (O'Keefe 2006), and has long been associated with memory (Scoville & Milner 1957). Anatomically, it supports large-scale interregional connectivity, consistent with a role in cross-modal association in support of episodic memory (Marr 1971; Teyler & DiScenna 1986). As a result, some of the initial discoveries about the hippocampus involved memory tasks in humans and often involved spatial navigation in rodent models as an ecologically valid mnemonic task.

In terms of spatial cognition, Edward Tolman was one of the first cognitive psychologists to build on previous work (e.g. Hull 1935) and directly challenge the approach of modelling behaviour in terms of simple stimulus-response relationships. Tolman developed some of the first theories that incorporated allocentric (world-model) based cognition instead of reactive (stimulus-response) based cognition. The results of his work led to theories how 'cognitive maps' might guide learning in many different areas of the brain (Tolman 1948). Not until O'Keefe and Dostrovsky discovered the 'place cell' in 1971, a hippocampal neuron that represents an environmental location, were these theories specifically applied to the hippocampus. O'Keefe & Nadel (1978) formulated these ideas in their book 'The Hippocampus as a Cognitive Map". The book was controversial in the field at the time, because the hippocampus was seen as an area that was associated with behavioural response

inhibition (Grastyan et al. 1959; Douglas 1969), and limbic system functions in emotion (Papez 1937). Conversely, human memory was seen as a purely egocentric process involving functions like episodic memory (Tulving 1972) and long-term declarative memory from famous studies like that of HM (Scoville and Milner 1957). Further adding to the confusion, long-term memory researchers found it difficult to relate their hippocampal lesion findings to prevailing ideas about the limbic system's role in response inhibition and emotion. Moreover, experiments recording from the rodent hippocampus, found that hippocampal activity in the theta frequency band, which is approximately ~6-10 Hz in rodents and ~4-8 Hz in primates was only linked to navigational motion (Grastyan et al. 1959; Vanderwolf, 1969).

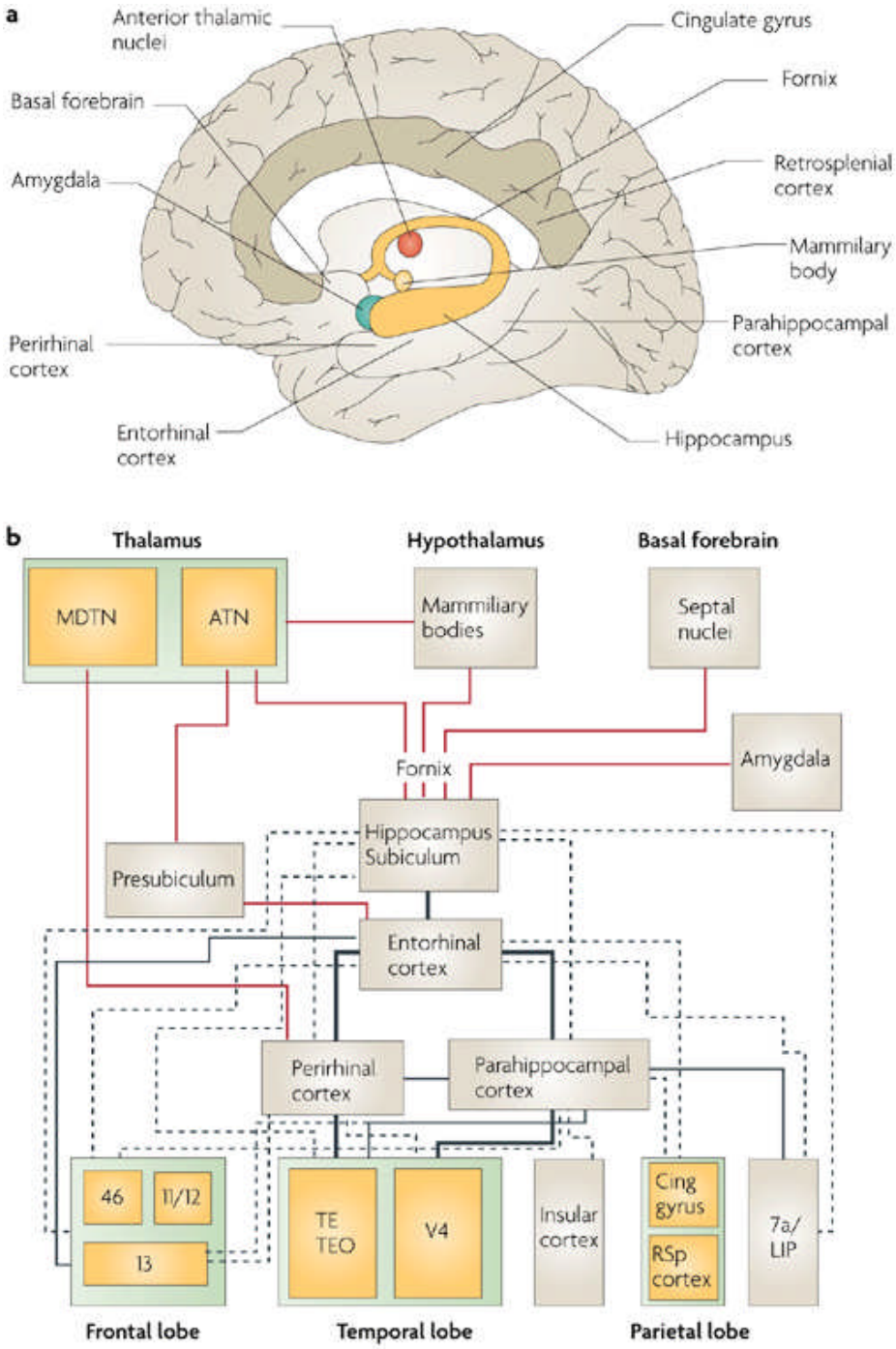

Figure 1: **Interregional connectivity of the hippocampal formation**
A schematic taken from Bird and Burgess (2008) *Nat Reviews Neurosci* showing connectivity between the hippocampal formation and the rest of the brain. A. Picture that shows the location of the hippocampus in relation to other structures in the medial temporal lobe (MTL). This picture emphasizes the location of the hippocampus relative to other structures in Papez's circuit (in yellow), including the mammillary bodies, the septal nuclei of the basal forebrain, the retrosplenial cortex and the parahippocampal cortex. B. Cortical and subcortical connectivity of the hippocampus. Cortical connections are indicated by black lines, while subcortical connections are indicated by red lines.

O'Keefe and Nadel's ideas eventually gained traction, and models of spatial cognition became more popular across cognitive neuroscience. This area of rodent electrophysiology has progressed with the discoveries of head direction cells (Taube et al. 1990), which code for the direction the animal is facing, and grid cells, which code for the animal's position relative to the vertices of a regular triangular grid over the environment (Hafting et al. 2005). Interactive spatial memory tasks were extended into human brain imaging over the last decade with both fMRI and intracranial electrophysiology (Maguire et al. 1998; Kahana et al. 1999). Notably, evidence of different types of hippocampal neuron types such as place, grid, and goal (neurons that only fire at a specific goal-directed location) cells have been found using intracranial and comparative human fMRI/rodent electrophysiology studies (Ekstrom et al. 2003; Doeller et al. 2010; Jacobs et al. 2011). An important aspect of using virtual navigation paradigms is that they can be applied in other animal models. For instance, an emerging technique is recording intracellularly in-vivo from mice during virtual navigation (Harvey et al. 2009). Recording from 'freely' behaving rodents intracellularly opens a host of new possibilities, including the ability to use techniques like optogenetics and molecular imaging to inform systems level interactions with functional neuroimaging (Dombeck et al. 2007). Yet even with similar paradigms and translatable findings from cellular to systems models of spatial navigation, the mapping of spatial navigation onto other aspects of cognition, such as episodic memory is a source of much confusion and debate (Buzsaki & Moser 2013).

I attempt to address the relationship between human and animal models of hippocampal function. In the literature review, the role of theta oscillations in movement, novelty, and spatial and mnemonic cognition is discussed. Further

background about the wider context of how hippocampal theta oscillations relate to systems neuroscience and the role of theta in cross-frequency coupling within and outside the medial temporal lobe is also provided. I will then provide an overview of novelty detection in the MTL and the differential contributions by MTL regions such as the hippocampus, amygdala, and parahippocampal cortex to learning about novelty. Further background on the parahippocampal cortex and spatial cognition is given to illuminate the role of other MTL regions outside of the hippocampus in spatial cognition. I will also review the role of low-frequency endogenous BOLD oscillations and what they can tell us about memory formation. I also briefly introduce some of the fMRI and MEG methodology used in my experiments. Afterwards, I then detail four experiments that address each of the topics discussed in the literature review.

I conclude by discussing the potential implications of these findings, including the relationship between the hippocampal theta rhythm and cognition, the behavioural relevance of cross-frequency and interregional oscillatory coupling, novelty processing by the human medial temporal lobe, and the behavioural relevance of the default mode network.

This thesis contains work detailed in the following peer-reviewed publications, book chapters, and conference abstracts

Publications

- **R Kaplan**, CF Doeller, GR Barnes, V Litvak, E Duzel, PA Bandettini, & N Burgess (2012) Movement-related theta rhythm in humans: coordinating self-directed hippocampal learning. ***PLoS Biology***, 10(2):e1001267

- CF Doeller & **R Kaplan** (2011) Parahippocampal Cortex: Translating Vision into Space. ***Current Biology,*** 21:589-91

- **R Kaplan***, D Bush*, M Bonnefond, PA Bandettini, GR Barnes, CF Doeller & N Burgess (under review) Medial prefrontal theta phase-locking coordinates spatial memory retrieval. *equal contributors

- **R Kaplan**, AJ Horner, PA Bandettini, CF Doeller, & N Burgess (submitted) Separating the content from the context: novelty processing in the temporal lobe.

Book Chapters

- C Lever, **R Kaplan &** N Burgess (In Press) 'The function of oscillations in the hippocampal formation' in Space, Time, and Memory in the Hippocampal Formation. eds: Derdikman D & Knierim J

Selected Abstracts

- **R Kaplan**, WM Luh, C Doeller, N Burgess, P Bandettini; UCL-NIMH "A 7T resting state fMRI study of MTL-Neocortical Connectivity Changes after Spatial Learning" Organization for Human Brain Mapping abstract 2012; Beijing

- **R Kaplan**, C Doeller, P Bandettini, & N Burgess; UCL-NIMH "Subsequent memory and the maintenance of spatial representations over different time scales" Society for Neuroscience abstract 2011; Washington, DC

Chapter 2

Neural oscillations and novelty processing in memory

2.1 The hippocampal theta oscillation

The theta frequency oscillation was one of the first neural oscillations observed in humans in the 1920s and 1930s by Hans Berger and was implicated with states of arousal. In the 1950s and 1960s, there were the first electrophysiological recordings from awake behaving animals and it was in this setting that hippocampal navigation-related theta was one of the first oscillations measured directly measured from the brain (Grastyan et al. 1959; Vanderwolf 1969). Hippocampal theta is critically dependent on the medial septum (see Bland & Oddie 2001; Buzsaki 2002), even though later work determined that the hippocampus to a lesser degree could generate autonomous theta (Traub et al. 1989). In one of his first observations about hippocampal theta, Vanderwolf found an increase in theta power when the rat initiated a voluntary movement (1969). Vanderwolf's laboratory later characterised two types of theta, broadly speaking, Type I voluntary locomotor theta, which is atropine resistant and Type II involuntary theta, which is atropine sensitive (Kramis et al. 1975). Interestingly, a lower frequency theta has also been seen during REM sleep (Irmis 1974). However the behaviour where theta is seen most strongly in the rodent hippocampus is during navigation, where it dominates oscillatory activity relative to other frequency bands (O'Keefe & Nadel 1978). The cognitive implications of the theta rhythm are unclear, albeit with a few important exceptions (for example see Winson 1978). However, by applying the same tasks as rats when recording from the human hippocampus more answers might be found. Over the past thirty years, there has been a build-up of literature investigating theta and its relationship to translational motion and novelty (for reviews see O'Keefe 2006; Burgess 2008; Duzel et al. 2010). When discussing theta, I will narrow down its potential links to those two aspects of exploration, novelty (namely environmental

novelty) and movement in rodent and primate models. I will then further discuss the possible role of theta oscillations in other aspects of cognition with a specific focus on memory.

2.2 Movement-related theta, place cells, and novelty

The interaction between hippocampal theta and exploratory movement is best captured by the activity of place cells in a phenomenon called theta phase precession (O'Keefe & Recce 1993; Skaggs et al. 1996). A place cell discharges when it enters its place field (the particular location where the cell fires) at a late phase of the LFP theta rhythm relative to the trough (where the overall firing is maximal). As the rat progresses through the field the cell will fire at earlier and earlier phases until it fires at 180-360 degrees earlier on exiting the field (O'Keefe & Recce 1993). Thus the rhythmic discharge in the place field is at a slightly higher rate than the ongoing theta rhythm. Other consequences of phase precession include a forward sweep through the environment of the location represented by place cell firing during each theta cycle (Burgess et al. 1994; Skaggs et al. 1996), which has been highlighted as a potential mechanism for preplay of future trajectories at decision points during rodent maze navigation (Johnson & Redish 2007; Gupta et al. 2012).

The relationship between theta and place cells provides a model for studying the neural processing of novelty. Place cell firing fields remap (i.e. change the position of their receptive field and/or firing rate) in novel environments (Bostock et al. 1991; Lever et al. 2002) and further experiments show that this remapping is governed by attractor dynamics (i.e. place cell firing is tolerant to subtle changes in environment up until a certain point, where remapping for a novel environment then occurs; Wills et al. 2005). Furthermore, a reduction of theta frequency was observed

in rats when they are placed in a novel environment (Jeewajee et al. 2008). Together these findings demonstrate the importance of contextual information beyond movement in determining theta activity in the hippocampus and when related to the previous findings by Winson (1978), hint at a close relationship between theta and memory. Additionally, these findings lend credence to the idea that encoding and retrieval in the hippocampus occur at different phases of theta from different inputs (Hasselmo 1995; Buzsaki 1996; Douchamps et al. 2013).

The relationship between memory and theta has been studied in the context of recognition memory and novelty. There have been many ERP studies that looked at the correspondence between theta and recognition of whether a stimulus is novel or familiar (for a summary see Rugg & Coles 1995). There is a consistent EEG effect of frontal-midline theta during correct judgements of whether an item/stimulus is previously seen or not (Klimesch et al. 2000). Also, there is an extensive literature of intracranial studies looking at hippocampal responses to novel stimuli (Halgren et al. 1980; Knight 1996; Fried et al. 1997; Grunwald et al. 1998). Intracranial recordings from the human hippocampus during remember/know judgements have shown an increase in single cell firing in the theta range in relation to the encoding of novel stimuli (Rutishauser et al. 2006). Furthermore, iEEG experiments have implicated the importance of the timing of hippocampal ERPs during memory encoding (Fernández et al. 1999b). Interestingly, during novelty judgements of past remembered items (i.e. judging whether they had previously seen a picture a previous learning phase before), the strength of theta phase-locking in medial temporal lobe neurons prior to encoding predicts successful memory recall (Rutishauser et al. 2010). Overall these findings provide a link between theta oscillations and memory function in the hippocampus. Although previously there

have been no comparable findings in humans for environmental novelty, unlike memory judgements for novel stimuli (Duzel et al. 2010).

2.3 Theta and cognition

It has been difficult to define a separate role for theta in purely cognitive function in rodents, independent of its role in self-initiated motion. Original work by Jonathan Winson (1978) explored the role of the theta rhythm and mnemonic performance. In rodents, Winson found that abolishing the source of the hippocampal theta rhythm by lesioning the medial septum, impaired rodents' performance on a spatial memory task in comparison to animals without lesions that still exhibited the theta rhythm (Winson 1978). Furthermore, more recent studies tried a similar approach, but looked at grid cell firing in the medial entorhinal cortex, and found that medial septum lesions stopped grid cell firing, implicating the theta rhythm (Brandon et al. 2011; Koenig et al. 2011). Nonetheless, the medial septum is critical for both cholinergic innervation of the hippocampus and for the hippocampal theta rhythm, and these aforementioned studies could be explained by disruption to either. Indeed, studies have found it difficult to disambiguate hippocampal theta contributions to movement from contributions to cognition (Kelemen et al. 2005; Shin et al. 2011). However, during translational motion some cognitive effects have been observed, like increased interregional theta coupling when rats come upon a choice point in a maze (see Jones & Wilson, 2005a and Benchenane et al. 2010 for examples), and effects of memory have also been observed with freezing during fear conditioning related to theta coupling between the amygdala and hippocampus (Seidenbecher et al. 2003).

Virtual navigation studies of the human hippocampal rhythm in humans may hold more promise, since they can explicitly test cognition (Kahana et al. 1999). Work from the laboratory of Michael Kahana has confirmed the presence of the theta rhythm during virtual navigation in patients with intracranial electrophysiology implants (Kahana et al. 1999; Caplan et al. 2003; Ekstrom et al. 2005; Jacobs et al. 2010), but most recordings of the hippocampus have only found transient theta related to navigation (Ekstrom et al. 2005). This discrepancy has also been found in non-human primates (Stewart & Fox, 1991; Watanabe & Niki 1985), even when primates are actively moving around their enclosure (Rolls et al. 1997; Georges-Francois et al. 1999; Hori et al. 2003, 2005). So far, the type I theta rhythm and cognition in humans has also been elusive. Promising evidence may come from patients with mammillary body lesions (paralleling medial septum lesions in rats), who appear to have severe memory impairments (Vann & Aggleton 2004). Moreover, lesions to head direction areas in both human neuropsychology and rats seem to have no effect on memory performance and theta respectively (Vann & Aggleton 2004; Vann 2010; Vann et al. 2011), which suggests that mammillary body lesions disrupt the generation of hippocampal theta. Still, it is important to note that there is an extensive human neuropsychology (Abrahams et al. 1997; Bohbot et al. 1998; Spiers et al. 2001) and fMRI literature (Maguire et al. 1998; Iaria et al. 2003; Wolbers & Buchel 2005; Doeller et al. 2008b, 2010; Igloi et al. 2010) demonstrating the involvement of the posterior right hippocampus in virtual spatial navigation tasks, particularly for memory performance on these tasks. Later in this chapter, theta and mnemonic function during non-exploratory tasks will be further discussed.

Outside of the hippocampus, there has been more success at linking theta to cognition, where there is a growing literature of theta band coherence in non-human

primates (Lee et al, 2005; Liebe et al, 2012) predicting short-term memory performance. Lee and colleagues observed that extrastriate cortical (V4) theta phase-locking during the delay period of a working memory task. Building on these findings, Liebe et al. found that theta phase-locking between dorsolateral PFC and V4 (extrastriate cortex) also predicted successful memory retrieval in a similar task. These findings suggest that theta oscillations help interregional and within-region coordination of memory retrieval. Theta activity related to behavioural performance has also been found in other regions of the MTL. Furtak and colleagues recorded from the rodent postrhinal cortex during an object-location task and found that theta power there was increased after incorrect object location decisions (Furtak et al. 2012).

Evidence from primate models, and some from rodents, indicates the presence of a strong frontal midline theta rhythm. Of all species, frontal midline theta is most prominent in humans (for review see Mitchell et al, 2010). EEG measurements of frontal midline theta are observed in a variety of tasks ranging from learning and memory, attention, decision-making and meditation (for review see Mitchell et al. 2010). Frontal midline theta has been source localized with MEG corresponds to either the anterior cingulate cortex (Asada et al. 1999), or medial prefrontal cortex (Ishii et al. 1999; Asada et al. 1999) depending on the study. Additionally, frontal midline theta also a prominent rhythm observed during rest (Mitchell et al. 2010). In a variety of EEG studies of memory, frontal midline theta is seen as an analog of the rodent hippocampal theta rhythm (Klimesch et al. 2001; Addante et al. 2011). Notably, the frontal midline theta rhythm has also been observed in awake behaving rodents and couples with the posterior midline (Young

& McNaughton 2008). However, the cognitive relevance of the frontal midline theta rhythm is still unclear.

Ignoring the apparent gap in animal models of theta and memory, there have been many promising human electrophysiological findings which were inspired by a working memory model (Lisman & Idiart 1995). Earlier studies have focused on using paradigms like the Sternberg working memory task to investigate working memory maintenance. Theta oscillatory activity during working memory has been reported in the human hippocampus using MEG (Tesche and Karhu 2000) and also iEEG (Raghavachari et al. 2001). A hippocampal source of theta during working memory has been supported by MEG studies of patients with bilateral hippocampal atrophy (Cashdollar et al. 2010), in which the patients were impaired at retaining associative information and showed reduced occipital-temporal theta synchrony compared to healthy control participants.

Following the identification of theta networks in WM maintenance, there have also been studies looking at declarative memory encoding. These studies have mainly focused on correlating theta activity with encoding and subsequent memory performance. Osipova and colleagues found that successful encoding and retrieval of remembered items correlated with occipital and right temporal theta activity (Osipova et al. 2006). One MEG study found that subsequent memory performance correlated with pre-stimulus MTL theta during memory encoding (Guderian et al. 2009), while another found that theta amplitude, including signal attributed to the MTL, was higher for recollection than recognition (Guderian & Duzel 2005). Parallel findings relating theta to subsequent memory have been made with intracranial hippocampal recordings (Sederberg et al. 2003, 2007) and with combined fMRI/EEG (Sato et al. 2010). These subsequent memory effects have also

been observed with hippocampal gamma power (Sederberg et al. 2007). Finally, a transient increase in hippocampal theta for encoding of unpredictable compared to predictable events in an iEEG study has also been found (Axmacher et al. 2010a).

Success with recognition, declarative and working memory has also been accompanied by a few attempts at translating spatial navigation theta findings into the human electrophysiological domain. With the success of several neuroimaging studies looking at spatial navigation in the late 1990s (Maguire et al. 1998; Epstein et al. 1998), and studies that demonstrated increased hippocampal theta activity during navigation intracranially (Kahana et al. 1999; Ekstrom et al. 2005) there has been a drive for non-invasive research into large scale theta dynamics using MEG in healthy volunteers. Several studies that have investigated MTL theta oscillations with MEG (de Araujo et al. 2002; Cornwell et al. 2008) utilising new source reconstruction techniques like beamforming (detailed in methods review section 3.5) to look for deep brain structures over longer time epochs. Cornwell et al. observed an increase in hippocampal theta with goal directed movement versus aimless movement and also that hippocampal theta correlated with performance in navigating a virtual reality Morris water maze. Navigation tasks show potential to be also applied to psychiatry, where a similar task has been adapted to depressed patients (Cornwell et al. 2010) and fear conditioning research (Cornwell et al. 2012) using a video game version of the Morris Water Maze (Morris 1984).

2.4 Exploration and self-directed learning

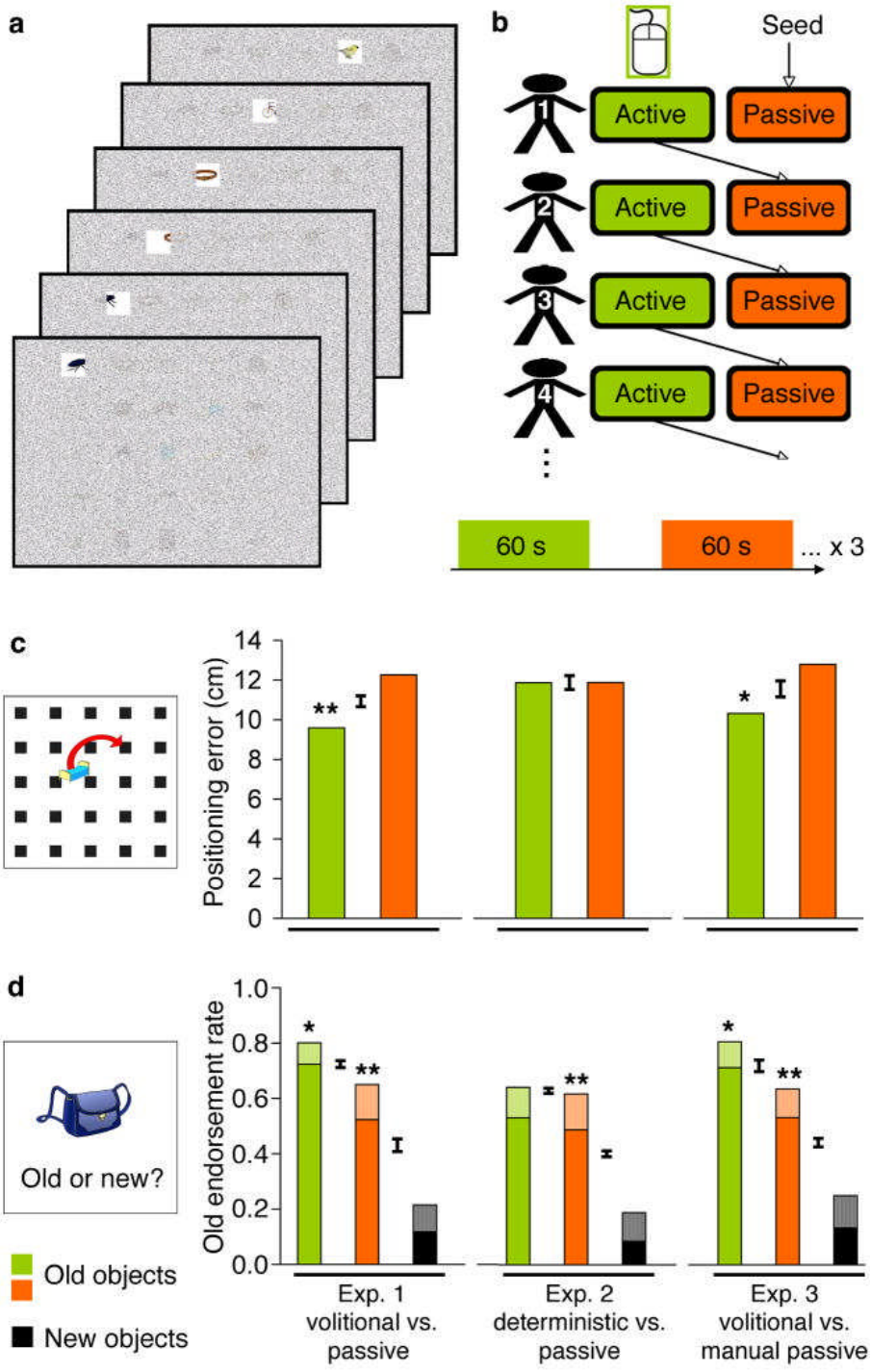

Figure 2: Self-directed learning in the hippocampus
Shows a schematic taken from Voss et al. 2012 Nature Neuroscience. Objects were viewed through a moving window, shown here (a) moving rightward to uncover the topmost row of objects in a 5×5 grid. Window position was under continuous active control for half of the object arrays and was delivered passively for the other half (b). Passive positions were determined by the active control of the previous experimental subject, so that object viewing was matched across conditions. Results are shown for the spatial recall memory test (c) and for the object recognition memory test. All experiments involved self-controlled (active) and passive viewing, with the task

requirements for each condition varied across experiments as indicated in the text. High-confidence responses for the object recognition test are indicated with solid bars and low-confidence responses with dithered bars. Error bars indicate the standard error of the difference between conditions represented by adjacent bars, and therefore correspond to the within-subjects statistical tests employed. *P<0.05 versus the right-adjacent condition. **P<0.01 versus the right-adjacent condition.

Another interesting application of the movement related theta rhythm to cognition might come from research on human self-directed learning. Work by Voss and colleagues (2011) has indicated that active learning during a memory task is hippocampal-dependent, while passive learning is not. The authors used a yoked visual search task similar to navigation, where objects were located in different parts of a virtual pegboard (presented on a computer screen). Participants when viewing the pegboard could either choose what objects they learned (active learning) or have the object chosen for them (passive learning). Hippocampal amnesics showed no deficits on the passive learning task, but did for the active learning component, while healthy controls showed improved performance on the active learning component with similar performance on passive learning as the amnesics. Furthermore, in a follow-up fMRI task in healthy controls, Voss and colleagues found a volitional control network centred on the hippocampus that corresponded to active versus passive learning. A potential role for hippocampal theta signalling the active learning of sequences is supported by experiments demonstrating that type I theta in rats is stronger when they are freely navigating versus when they are strapped to a motorised cart and passively moving through a maze (Song et al. 2005; Terrazas et al. 2005). These findings along with other behavioural results from human self-directed learning (Gureckis et al. 2012) might unlock a key role linking the hippocampus to exploratory movement in humans.

2.5 The hippocampal and mPFC theta rhythms

One of the primary areas that shows theta phase coupling with the rodent hippocampus is the medial prefrontal cortex (mPFC), a key area implicated in decision-making (for review see Rushworth et al. 2011). It is debatable whether it is even necessary to perform species matching between rodent and primate models in terms of hippocampal-mPFC interactions, since the PFC is much better developed in primates then it is in rodents (Gaffan 2002). Despite this lack of PFC conservation across species, many studies have investigated hippocampal theta coupling with the mPFC in rats running a t-maze (for early examples see Jones & Wilson 2005a; Hyman et al. 2005; Siapas et al. 2005). At decision points in the t-maze, Jones and Wilson (2005a) observed increased theta coupling between mPFC and hippocampus and more recent studies have found that mPFC-hippocampal theta coupling increases after learning (Benchenane et al. 2010). Additionally, other studies reported mPFC and hippocampal theta phase precession during exploratory movements (Jones & Wilson 2005b) and that mPFC neural firing alternates between coupling with the hippocampal theta rhythm and non-phasic firing (Hyman et al. 2005). The capability of mPFC neurons to phase-lock with the ongoing hippocampal theta rhythm is further highlighted by the finding that mPFC neurons most strongly phase-lock to hippocampal CA1 theta at a delay of about 50 ms and demonstrate a hippocampal lead in directionality with the mPFC during exploration (Siapas et al. 2005). Further findings have demonstrated timing differences and synchronization between mPFC and hippocampus that might aid in interregional communication between these two areas during conditioning (Paz et al. 2008).

Studies from Joshua Gordon's laboratory have shown theta coupling between mPFC and hippocampus during fear conditioning in rodents and found (Adhikari et

al. 2010; Adhikari et al. 2011) that correlated firing and theta activity in the ventral hippocampus with the mPFC increased in spatial locations that provoked anxiety in the rat. Building on previous work showing (Seidenbecher et al. 2003) amygdala-hippocampal coupling, these demonstrate the behavioural relevance of interregional communication via the hippocampal theta rhythm (most likely the type II theta rhythm). Related human electrophysiological findings have been rare, although recent ECoG (Anderson et al. 2010; Watrous et al., 2013) and MEG (Guitart-Masip et al. 2013) studies have observed PFC-MTL theta (and also delta and alpha) phase-locking. Furthermore, Watrous and colleagues have shown that the precision of 2 Hz coupling between PFC and MTL during spatial memory retrieval predicted spatial memory performance, while 8 Hz coupling between those same areas (Watrous et al. 2013). These recordings were from the surface of the parahippocampal gyrus and prefrontal cortex, but no related findings from human mPFC and the hippocampus have been presented so far. However, promising evidence from the human fMRI literature looking at the hippocampal-medial prefrontal dialogue implies that communication between these two structures is vital for memory retrieval (for review see Winocur et al. 2010) and research from rodents looking at long-term memory storage parallels these findings further (for review see Frankland & Bontempi 2005).

2.6 Gamma oscillations and memory gamma performance

It is thought that gamma oscillations are an important study of neocortical representations that are useful for memory. Many models posit that gamma oscillations are a mechanism for temporal coordination of different elements of memory (Jensen & Lisman 2005; Buzsaki 2006; Nyhus & Curran 2010), which fits

with gamma's perceived origin from local feedback inhibition (Middleton et al. 2008). Gamma activity has been mainly associated perceptually induced activity in visual cortex (Gray & Singer 1989; Tallon-Baudry & Bertrand 1999; Hall et al. 2006; Hoogenboom et al. 2006) across species. Furthermore, gamma band coherence is known to be relevant for behaviour (Womelsdorf et al. 2006). Based on these findings, current theories have highlighted the importance of 'communication through coherence' and task-relevant communication between different regions through phase-locking within the same frequency (Fries 2005, 2009). Concepts from 'communication through coherence' have been applied to the rodent hippocampus and to the investigation of how interactions between task-relevant regions might guide memory (Buzsaki 2006; Battaglia et al. 2011).

Gamma oscillations themselves have been implicated in memory, independent of their relationship to theta. For example, successful declarative memory formation is accompanied by gamma synchrony between the rhinal cortex and hippocampus (Fell et al. 2001). Desynchronisation of these two structures was accompanied by the inability to retain the memory. In a similar task, in non-human primate hippocampal recordings, Jutras and Buffalo observed that gamma synchronization during encoding of stimuli in a recognition memory tasks, predicted whether stimuli would be successfully remembered (Jutras & Buffalo 2009). Furthermore, in a recent MEG experiment Niewenhuis and colleagues (2012) found that learning new semantic associations increase high gamma (60-140 Hz) power correlations between task-relevant regions and the anterior temporal lobe.

2.6.1 Cross-frequency coupling and the hippocampus

In systems neuroscience, there is a wide-ranging literature on cross-frequency coupling, involving modulation of the power of a faster frequency by the phase of a slower one, usually within the neocortex (details explained further in Chapter 3 Methods review).

Theta-gamma coupling is often hypothesized to function in a master-slave relationship, implying that theta might function as an instrument of sensory selection (Lakatos et al. 2008; Buzsaki 2006). Informed by theoretical work hypothesizing that the hippocampus serves as a comparator (Vinogradova 2001), Colgin and colleagues (2009) found that different gamma frequencies in the medial entorhinal cortex (~65-120 Hz) and CA3 (~25-50 Hz) couple with the ongoing theta rhythm in CA1 in awake behaving rodents. Notably, these different gamma sources are usually phase-locked to different phases of the ongoing CA1 theta rhythm, and tend to occur in different cycles. Previous studies had found a lower frequency (25-50 Hz) gamma rhythm in CA3 than in medial entorhinal cortex (Bragin et al. 1995), and that (40-100 Hz) gamma phase coupling between CA3 and CA1 was higher during awake behaviour than REM sleep (Montgomery et al. 2008). Additionally, Montgomery and colleagues (2008) found that both theta and gamma phase coupling increased between CA3 and dentate gyrus during REM sleep. Furthermore, recent work has found that increased CA3-CA1 gamma synchrony predicted increased precision of place cell replay in the awake rodent (Carr et al. 2012). The capability of the CA1 theta rhythm to couple with different frequency oscillations is further supported by work from Belluscio and colleagues (2012) who found that CA1 theta phase coupled with the amplitude of slow (30-50 Hz), mid-frequency (50-90 Hz) and fast gamma (90-150 Hz) frequencies both during maze exploration and REM sleep. Cross-frequency coupling between the hippocampal formation and other regions has also

been found. Tort et al. (2008) found that striatal (~110-150 Hz) gamma amplitude was modulated by the ongoing hippocampal theta phase around the onset of T-maze trials. Furthermore, Sirota et al. (2008) found that neocortical gamma rhythms with different neocortical sources and different frequencies occurred at different phases of the ongoing hippocampal theta rhythm in the freely behaving rodent.

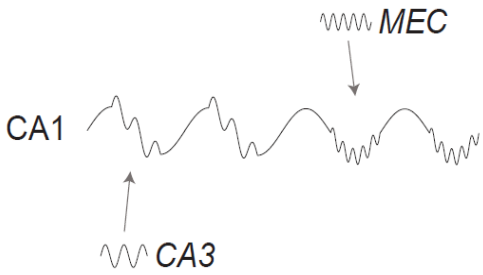

Figure 3: The theta-gamma dialogue in the hippocampal formation
Shows findings from Colgin and colleagues demonstrating how fast gamma from the MEC and slow gamma from CA3 have a specific phase relationship to the theta oscillations of CA1 (Colgin et al. 2009) .

Tort and colleagues observed hippocampal theta modulation of striatal gamma amplitude, most prominently during decision-making periods in t-maze exploration (Tort et al, 2008). Furthermore, theta-gamma coupling within CA3 of the hippocampus correlated with successful memory performance of item-context binding in rats (Tort et al. 2009). Taken together, these studies suggest that the theta rhythm provides a temporal coordinating mechanism between brain regions for binding different representations to memory.

Similar results with cross-frequency coupling have also been found in humans, where theta-gamma coupling was observed during successful encoding in the rhinal cortex and hippocampus during memory retrieval (Mormann et al. 2005). In a MEG study, Fuentemilla et al. (2010) applied pattern classifiers to theta and

gamma activity elicited during encoding for individual stimuli and subsequently decoded their replay during working memory maintenance. Replay of different stimuli categories (e.g. whether particpiants were maintaining a picture of an indoor or an outdoor scene) was decoded during maintenance and the replay of maintained items was usually locked to the theta phase and the consistency of decoded items with theta phase correlated with memory performance. In follow-up analyses, performance correlative theta power during working memory maintenance was source localized to the hippocampus and dorsolateral prefrontal cortex (dlPFC) (Poch et al. 2011). Further evidence of the importance cross-frequency coupling during working memory maintenance comes from a paper by Axmacher and colleagues, who observed theta-gamma coupling during working memory maintenance in patients with hippocampal depth electrodes (2010b). The authors also demonstrated that the consistency of hippocampal theta-gamma coupling predicted memory performance, extending the behavioral relevance of cross-frequency coupling (Axmacher et al. 2010b). Although human oscillatory findings with declarative and working memory have been found, as of yet, there have been no similar findings to previous rodent navigation findings, despite their similar oscillatory coupling dynamics showing theta-gamma phase synchrony.

2.7 Human MTL novelty processing

The human MTL, particularly the anterior hippocampus and amygdala, have been implicated in novelty detection in iEEG studies (Halgren et al. 1980; Knight 1996; Rutishauser et al. 2010). These findings have been substantiated by human fMRI findings implicating the hippocampus in novelty detection (Stern et al. 1996; Strange et al. 2005; Kumaran et al. 2006). This echoes the hypothesised role of CA1

in the hippocampus as a comparator (Vinogradova 2001). However, whether the hippocampus is a generalized novelty detector (Sokolov 1963) or not, is an open question (for review see Ranganath & Ritchey 2012).

Most findings linking novelty with the hippocampus have primarily focused on the anterior hippocampus. A line of research in both fMRI (Strange et al. 2005; Kumaran et al. 2006) and intracranial EEG (Halgren et al. 1980; Knight 1996; Fried et al. 1997; Rutishauser et al 2010) has related anterior hippocampal responses to novelty detection, usually focusing on associative mismatch and P300 responses respectively. The success of these paradigms has implicated the human hippocampus in prediction error, although evidence from animal models of the hippocampus is lacking in this area.

Many iEEG studies of novelty detection (and mnemonic function) (Fried et al. 1997; Rutishauser et al. 2010) lump together electrodes sites recording from the amygdala and hippocampus, which opens up the possibility that the amygdala may hold a specific role in novelty detection. In addition to human iEEG findings, a series of studies by Moses and colleagues have shown that amygdala lesioned rats have deficits on identifying proximal objects and detecting novel objects in an environment, (Moses et al. 2002, 2005). Conversely, the hippocampus was implicated in contextual memory performance and perirhinal cortex in detecting relationships between novel stimuli (i.e. where objects are located in relation to each other; Moses et al. 2005). Notably, the amygdala has been implicated in rodent object recognition (Farovik et al. 2011) and spatial novelty detection (Sheth et al. 2008).

Previous work (see Bagshaw et al. 1972 for an example) in primates has implicated the amygdala in visual orienting. These findings suggest a companion

role for the amygdala with the basal forebrain (an area which houses the medial septum) in surprise detection (i.e. a surprise omission of a familiar object in an environment; Gallagher & Holland 1994; Lin & Nicolelis 2008). The amygdala's role in surprise detection suggests that areas of the so-called 'extended amygdala' like the sublenticular substantia innominata function as part of a cholinergic system for processing salient stimuli (Alheid 2003). Notably, this is the same cholinergic system that is hypothesized to generate the hippocampal theta rhythm (Alheid 2003).

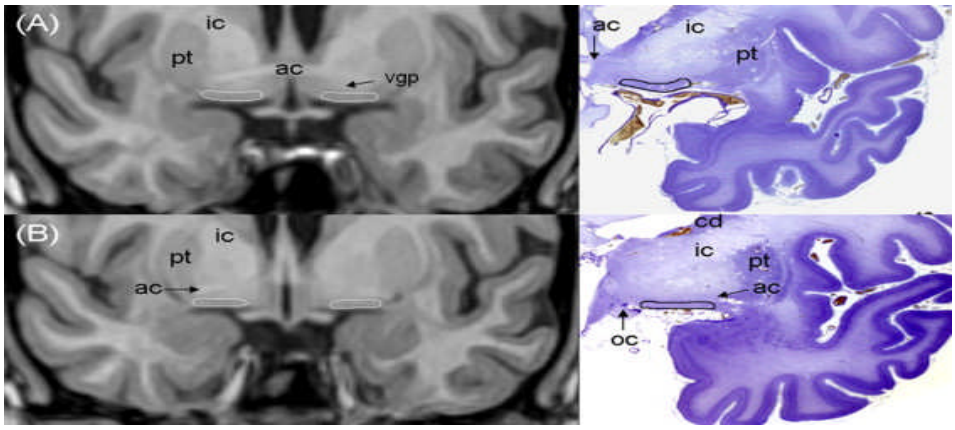

Figure 4: Human substantia innominata
Adapted from George et al. 2011, which shows that the human substantia innominata in the nucleus basalis region correlates with declarative memory performance (A) MRI scan showing the substantia innominata (left). Corresponding Nissl-stained coronal section of the left hemisphere of a post-mortem aged control brain showing the region of interest (right). (B) MRI scan showing a caudal section lobe (left). Corresponding Nissl-stained coronal section of the left hemisphere of a post-mortem brain showing substantia innominata (right). The outline (white, black) illustrates the segmentation of the region containing the SI. ac, anterior commissure; cd, caudate nucleus; ic, internal capsule; oc, optic chiasm; pt, putamen; vgp, ventral globus pallidus

In terms of connectivity, the human superficial/extended amygdala has been shown to project to the lateral orbitofrontal cortex (Bach et al. 2011), as opposed to the basolateral amygdala, which projects to polymodal areas in the temporal pole. The amygdala's connectivity with the cortex allows for the possibility that it could serve as a detector of not just fearful, but also ethiologically relevant stimuli (O'Keefe and Bourna 1969). The idea that the amygdala is a detector of

ethiologically relevant stimuli also fits well with the amygdala's known capability to process reward valence and social cues (LeDoux & Phelps 2005; Adolphs 2010; Morrison & Salzman 2010). Furthermore, the human amygdala function can be modulated by the type of environment (i.e. urban or rural) someone is raised in (Lederborgen et al. 2011) and a promising area of future investigation is how someone's upbringing could affect learning about novel information within a given environment.

Other areas of rhinal cortex, such as perirhinal cortex and post-rhinal cortex, are implicated in recognition memory in both animal (Aggleton & Brown 2001; Murray et al. 2007) and human (for review see Ranganath and Ritchey, 2012) memory. Yet, it is unclear whether recognition of novel of familiar content or contexts is dependent on functional networks including the rhinal cortex, amygdala, or the hippocampus, as opposed to the individual regions themselves, since most studies have focussed on dissociating between two MTL regions and not investigating the functional connectivity between them.

2.8 Parahippocampal cortex: translating vision into space

Perceiving our local environment is one of the brain's most crucial functions. The surrounding space is encoded initially in a first-person perspective; this 'egocentric' representation is transformed to encode relations between the viewer and external space. The latter, 'allocentric' representation is stored as an internally driven map-like guide that allows us to manipulate and navigate in the world. The parahippocampal cortex, located in the medial temporal lobe, has been consistently identified as supporting human orientation and navigation. In a seminal study, Epstein and Kanwisher (1998) showed that parahippocampal cortex preferentially

responds to scene stimuli, rather than single non-scene stimuli like objects or faces; it is particularly concerned with layout-defining spatial properties of scenes, including geometric features such as walls (Epstein 2008). Spatial scenes are complex stimuli and the extent to which precise features are encoded by parahippocampal cortex is still unclear.

Two studies (Mullally & Maguire 2011) and (Kravitz et al. 2011) provide new insights into how the parahippocampal cortex represents space. Both studies used functional magnetic resonance imaging (fMRI) in humans to test findings from different aspects of spatial processing (vision and spatial cognition). Mullally and Maguire (2011) show that simply imagining objects against a blank background activates the parahippocampal cortex, but critically only for those objects where participants have a strong feeling of surrounding space. Kravitz et al (2011) report that, during the perceptual judgement of real-world scenes, the parahippocampal cortex is selectively responsive to the spatial properties of the scene, but neither contextual nor categorical aspects. Additionally, a recent report shows that the parahippocampal cortex can support a visually independent internal representation of scenes perceived haptically in healthy and even blind participants (Wolbers et al. 2011).

This emerging literature suggests an exciting possibility of investigating both perceptual and mnemonic inputs to the parahippocampal region as an integrative area, or ‘translator’, between respective visuospatial and spatial representational systems (Burgess et al. 2001; Figure 1). The parahippocampal region's role as a translator towards integrating information from these two systems is consistent with its anatomy. The parahippocampal cortex in humans corresponds approximately to postrhinal cortex in rats and areas TF and TH in non-human primates (Witter &

Wouterlood 2002). It receives strong projections from visual cortex (and cortical association areas) and in turn provides a dominant input into entorhinal cortex and also projects to the subiculum and the hippocampal subfield CA1 (Witter & Wouterlood 2002).

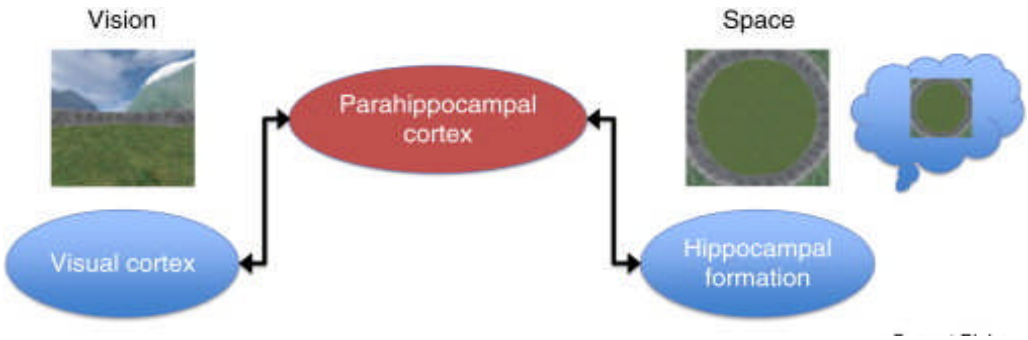

Figure 5: Parahippocampal cortex
Hypothetical roles of the visual cortex and hippocampal formation in processing a visual scene, which in this example is a virtual mountain environment. The visual system maintains an externally driven egocentric view of the environment, while the spatial representation system maintains an internal allocentric map and imagined perception of the same environment. This visuospatial information gathered about the environment is fed to the parahippocampal cortex, where it is integrated with information from the hippocampal formation's spatial representation system to create a hypothesized integrated sense of space. (Images of the virtual environment reproduced with permission from Doeller et al. 2010).

The parahippocampal cortex thus lies at the interface between the spatial representational system in the hippocampal formation and the visual system (see Figure 5), which makes it an ideal candidate to integrate external visual and internal spatial signals. The interaction between incoming sensory information and stored spatial representations has a cellular correlate. Single cells in the rat brain signal an animal's allocentric position in the local environment, suggestive of an internal cognitive map (O'Keefe & Nadel 1978). Two recently discovered cell types might be of particular relevance here: boundary-vector cells in the subiculum (Lever et al. 2009) and border cells in entorhinal cortex (and to a small extent also in the vicinity of postrhinal cortex) (Solstad et al. 2008). Interestingly, they were found in the two regions which receive direct input from postrhinal cortex. These cells

encode the animal's position relative to geometric features in the environment, like walls and corners. The functionality of these cells could relate to observations in the two fMRI studies that the space-defining object effect in the parahippocampal cortex is driven by lower portability and greater size, (Mullally & Maguire 2011) and also the finding that parahippocampal cortex activity reflects expanse (whether it is open or closed) of scenes (Kravitz et al. 2011; see also Epstein 2008; Bird et al. 2010; Park et al. 2011).

An interesting avenue for future research will be the investigation of how mechanisms of scene perception previously measured between the parahippocampal cortex and high-order visual areas in human and non-human primates — particularly the 'what' *versus* 'where' pathways (Ungerleider & Mishkin 1982) — correspond to findings in targeted electrode studies of rodents, human neuropsychology and neuroimaging studies implicating the hippocampal formation in active spatial exploration and spatial introspection (Burgess et al. 2001; Hassabis et al. 2007; Bird et al. 2010).

2.9 The overlap between spatial memory and resting state networks

The ability to imagine potential outcomes is a vital component of human cognition. Human brain imaging has allowed the investigation of which brain anatomy is associated with this type of planning, particularly focusing on the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and hippocampus (Buckner & Carroll 2007; Hassabis & Maguire 2007). On the other hand, recent developments in human brain imaging have shown that there are brain networks active independent of a particular stimulus (Raichle et al. 2001). One of the most robust networks of endogenous activity in neuroimaging is called the default mode

network (DMN), which also centres on the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and hippocampus (Raichle et al. 2001; Schacter et al. 2007; Buckner et al. 2008). As a result, there is significant interest in why and how task-free or endogenous fluctuations in brain activity might relate to behavior (Deco & Corbetta 2011).

2.9.1 Memory consolidation and the default network

Endogenously driven neural fluctuations over long time scales (i.e. hours to years) are thought to be particularly relevant to cognitive processes like memory consolidation. Through a neocortical-hippocampal dialogue, learned representations are hypothesised to be stored and dynamically altered spanning a time course from minutes to years (Frankland & Bontempi 2005; Winocur et al. 2010). Theoretical models suggest that communication between structures like the mPFC and hippocampus might reflect the optimization of competing internal models (i.e. stored representations), using itinerant neural dynamics over these long time scales to consolidate the memory of particular representations (Sadaghiani et al. 2010). These ideas suggest that functional connectivity between the hippocampus and the mPFC should change over time as the storage of the representation either becomes more precise and less labile, or vice versa. The observation by Peigneux and colleagues that BOLD activity in the hippocampus during unrelated tasks after learning could support memory performance was the first evidence in this direction (Peigneux et al. 2008).

These findings related to offline memory performance were followed by tasks with formal resting-state periods looking at various types of memory encoding (Stevens et al. 2010; Tambini et al. 2010; van Kesteren et al. 2010). The main goal of

these studies was to combine the approaches of performance-related resting state fluctuations (Lewis et al. 2009) with subsequent modulation of task-relevant networks associated with successful later memory recall (Peigneux et al. 2006). Tambini and colleagues (2010) found that increased hippocampal connectivity with fusiform areas after the encoding of face stimuli during rest and successful recall. Interestingly, van Kesteren and colleagues and found that vmPFC-hjppocampal connectivity during a resting period correlated with subsequent performance or retention of a tactile/visual association learned before that period. This experiment examined the consolidation of schemas, in this instance an association between tactile stimuli and semantic information presented on a screen. Moreover, the human sleep literature has found fMRI and electrophysiological evidence of the importance of offline states in consolidating previously learned representations (Diekelmann & Born 2010). Increased connectivity among these same default network nodes, and corresponding slow oscillatory activity, has been observed to correlate with memory performance and learning retention during the waking state (Gais et al. 2000; Rasch et al. 2007; Diekelmann & Born 2010). Numerous hypotheses from the animal sleep literature (Vyazovskiy et al. 2008) speculate about neuronal maintenance processes like synaptic homeostasis that parallel hypotheses about memory consolidation.

Evidence for changes in endogenous activity related to memory consolidation is further supported by animal electrophysiology literature showing schema-related consolidation, although it should be noted that most work on schema-related consolidation is with lesion/inactivation studies (Wang and Morris 2010). These ideas are additionally corroborated by evidence of synaptic tagging of hippocampal-cortical memory networks after initial memory encoding (Lesburgueres et al. 2010).

Another hypothesis about offline consolidation of previously learned memories is that it is aided by high-frequency sharp-wave 'ripple' activity. Measuring ripples and disrupting them during waking state and sleep in rodents correlates with decreased subsequent memory performance (Girardeau et al. 2009; Jadhav et al. 2012). Another correlation of ripples with subsequent memory performance has also been found during human sleep (Axmacher et al. 2008). Furthermore, a study by Logothetis and colleagues found high-frequency ripples in the primate hippocampus, and found that there was a decrease in neocortical BOLD activity during ripple events (Logothetis et al. 2012). The functional relevance of endogenous brain activity to spatial memory consolidation is further strengthened by the observation by Wegman and colleagues, of increased parahippocampal-hippocampal connectivity compared to pre-experimental resting state after learning correlating with navigational ability (Wegman et al. 2012)..

The idea that ongoing activity could be used to characterize behavioural ability has been especially well received in clinical research, where patients might have difficulty performing normal tasks within the scanner. Measurements of baseline PET metabolism were originally correlated with memory-related cognitive impairment in elderly adults (Desgranges et al. 1998). Other electrophysiology related memory findings have their foundations in ERP research (Otten et al. 2006) and ongoing alpha oscillations (van Dijk et al. 2008). A major difficulty in memory research is the constant fluctuation of hippocampal activity (Stark & Squire 2001), but one study cleverly used spontaneous fluctuations in ongoing hippocampal BOLD activity and correlated it with later ability on a memory task (Wig et al. 2005). Dickerson and colleagues followed-up the PET experiments by using resting state fMRI to characterize behavioral performance on memory tasks. They observed that

increased interhemispheric hippocampal effective connectivity predicted memory recall in healthy volunteers whereas increased hippocampal-precuneus effective connectivity predicted memory recall in healthy older adults (Dickerson et al. 2010). These findings highlight the potential to harness 'wandering baseline' activity (Stark et al. 2001) to better understand endogenously driven influences on memory encoding and recall.

The importance of prestimulus activity (activity during the inter-trial interval immediately preceding encoding) with successful memory storage is now well-documented within the memory literature (Otten et al. 2006; Guderian et al. 2009; Gruber et al. 2010; Park et al. 2010; Rutishauser et al. 2010). Unfortunately, the links between prestimulus related-memory effects in humans and the rodent spatial memory literature are not as clear. This dearth of links is particularly apparent when examined in comparison with the behavioral correlates of consolidation-related changes, particularly during sleep (see review by Marshall & Born 2007). Currently, there is little evidence of performance-related neocortical-hippocampal synchrony prior to task performance during offline non-sleep states. Nonetheless, in rodents high frequency ripple related "preplay" activity of place cells during offline periods corresponds to spatial sequences of place cell firing that are subsequently expressed in a new environment (Wilson & McNaughton 1993; Dragoi & Tonegawa 2011).

2.9.2 Interim Summary

The seemingly disparate topics of movement-related theta oscillations, MTL function, and novelty processing in the review are coming closer together through the link between oscillations and behaviour. A key link between novelty processing to the hippocampus and its oscillatory activity is that they are both thought to be

driven by the same source, cholinergic inputs from the basal forebrain. How these capabilities extend to other medial temporal lobe regions and surrounding brain networks is also an open question. Investigating oscillatory activity and novelty processing during active learning (i.e. spatial navigation) will be the topic of my research.

Chapter 3

Methods

3.1 Methods Review

Two methodological approaches were implemented in my thesis work. Experiment 1 used fMRI and MEG to elucidate the role of the hippocampus and 4-8 Hz theta rhythm respectively in virtual movement during an interactive spatial memory task. Experiment 2 used MEG to investigate interregional and cross-frequency theta coordination of spatial memory retrieval. Experiment 2 was analysed using MEG source reconstruction techniques along with source connectivity techniques. Experiment 3 investigated different types of novelty during virtual navigation using whole-brain fMRI. Experiment 4 looked at resting-state fMRI and its behavioural correlates in spatial learning using both standard 3T scanning and ultra high field 7T scanners.

For this chapter, I will provide an introduction to some emerging concepts in fMRI and a general overview of MEG. When discussing fMRI, I will also briefly go over resting state analysis in fMRI and ultra high field (>3T). For an overview of the basic concepts and methods behind fMRI not discussed in this chapter, I suggest books by Huettel, Song and McCarthy 'Functional Magnetic Resonance Imaging' (2009), and the "Handbook of Functional MRI Data Analysis' by Poldrack, Mumford and Nichols (2011). Additionally, 'Statistical Parametric Mapping: The analysis of functional brain images' by Friston, Ashburner, Kiebel, Nichols and Penny (2006) provides a general description of the SPM approach to image analysis that is used in all of my experiments. When discussing MEG, I will also provide an overview of source reconstruction and connectivity techniques. Detailed descriptions of standard MEG analyses are given in Chapter 4 and MEG source reconstruction in Chapters 4 and 5. Chapter 5 also fully discusses the MEG source connectivity analyses.

3.2 The origin of the BOLD signal

In the past few decades, functional magnetic resonance imaging (MRI) has been used extensively to non-invasively measure human brain activity with relatively high spatial resolution and interpretable temporal resolution. An fMRI scanning sequence measures the blood-oxygen level-dependent (BOLD) signal, which depends on the balance of oxygenated versus deoxygenated glucose in the blood. Based on echo-planar imaging developed by Mansfield (1977), fMRI was first used by Belliveau and colleagues (1991) using intravenous injections of contrast agent (gadolinium). Soon after several groups (Bandettini et al. 1992; Kwong et al. 1992; Ogawa et al. 1992) developed non-invasive BOLD fMRI imaging techniques which are still used currently. I will detail some more about the interpretation of the BOLD signal in activation studies, particularly in comparison to the MEG signal.

Potential neural origins of fMRI activty

The neural basis of the fMRI signal remains unclear, but experiments by Heeger and Ress explored the lag between the haemodynamics of the BOLD signal and the spiking activity of neurons (Heeger & Ress 2002). The vasodilation caused by oxygenation is usually generated about one second after initial neural activity (Heeger & Ress 2002) and this vasodilation is thought to cause the BOLD effect typically measured with fMRI (Logothetis 2002). Logothetis found that high frequency gamma power, measured from the LFP of visual cortex in primates, positively correlated with the BOLD signals and that the signal to noise ratio of neural activity was much higher than the haemodynamic response (Logothetis et al. 2001). Human simultaneous fMRI/EEG studies have replicated the correlation of BOLD with gamma and also have found negative correlations in lower frequencies

(Meltzer et al. 2009; Ekstrom et al. 2010; Scheeringa et al. 2010). Notably, BOLD activity in the human hippocampus appears to be decorrelated with theta power (Ekstrom et al. 2009), despite findings in the rodent hippocampus that shows oxygen tissue concentration positively correlates with theta power (McHugh et al. 2008). Petridou and colleagues attempted to measure neural activity in rat brain cultures at 3T and 7T and found that neural excitation paralleled increases in the BOLD signal (Petridou et al. 2006). With techniques like neural event triggered fMRI (NET-fMRI) in invasive primate recordings (Logothetis et al. 2012), the relationship between electrophysiological phenomena such as ripples can subsequently characterized by the effect of a neurophysiological 'event' on BOLD activity across the whole brain. The field of fMRI research still has several outstanding issues, namely the differentiation of inhibitory neural activity from excitatory activity, BOLD signal change not being a quantitative measure, and the relatively slow pace of haemodynamic factors compared to neural activity (Bandettini 2009). However, combining electrophysiological recordings either simultaneously during fMRI acquisition or separately (like with MEG in Chapter 4) with fMRI experiments can help move the field beyond these issues.

3.3 Ultra High Field fMRI

In addition to parallel imaging, which combines the signal from multiple coil arrays, thus shortening acquisition time and leading to faster repetition time or TR, higher fields can provide increased temporal and spatial resolution (Ugurbil et al. 2003). The necessity of a regular structural image might be eliminated with the use of high enough resolution echo planar imaging (EPI) sequences, since brain anatomy is observable from a high-resolution 7T sequence. Furthermore, high resolution

provides the opportunity to better examine subregions of areas, like the subfields of the hippocampus, which have been difficult thus far (Wisse et al. 2012). Techniques such as 7T increase signal to noise, but pick up unrelated physiological artefacts, thus making pulse/heart-rate and breathing data crucial for fMRI acquisition (Bandettini et al. 2012). Furthermore, because of the extremely powerful magnetic fields and small bores for participants to lie in, peripheral nerve stimulation, dizziness, and a metallic taste in the mouth have been common issues (Bandettini et al. 2012). However, with advances in technology and the vast potential of ultra high field imaging, higher field scanners appear poised to become useful tools in cognitive neuroscience.

3.4 Resting State fMRI

Early fMRI activation studies compared different behavioral conditions against a baseline to measure the neural correlates of cognition. However, there were lingering doubts about whether the 'baseline' in fMRI was truly a non-cognitive state. Bharat Biswal and colleagues (1995) found that the 'resting' or baseline signals in left and right motor cortex were correlated despite their distance. This was the first suggestion that there was coordinated activity across cognitively relevant brain networks in the absence of a task. Building on this evidence with task-free PET and fMRI data, Marcus Raichle and colleagues proposed that there was a default mode network (DMN), encompassing the mPFC, MTL, temporal pole, lateral parietal lobules and posterior midline, which showed a consistent reduction in the BOLD signal during tasks compared to baseline (2001). However, as mentioned earlier, not all tasks showed deactivations in these areas, particularly during episodic memory and spatial navigation tasks (for review see Hassabis & Maguire 2007). Additionally,

there was heavy criticism that there was no such thing as baseline or resting period and that it was more likely to reflect mind wandering (for a useful summary of concerns about a default mode of brain function see Morcom & Fletcher 2006). However several findings helped overshadow these reservations, one seminal finding was the discovery of these networks in anaesthetized primates (Vincent et al. 2007) and another was the finding that resting-state networks exhibit the same spatial pattern over different time lengths or whether participants' eyes were open or closed (Fox et al. 2005). The field is still plagued by many issues including anti-correlated networks introduced by respiratory and heart rate artefacts (Birn et al. 2008; Murphy et al. 2009; Handwerker et al. 2012), and also introduced by signal drift and global signal regression (Fox et al. 2009; Murphy et al. 2009). Furthermore, another problem in clinical and developmental studies is head movement, which can vary by age and condition and give false changes in connectivity (van Dijk et al. 2012). However, with the richness of the data and further techniques and designs to incorporate these factors, this area of research holds great promise in the future.

I will now briefly summarize the steps that go into resting state analysis (some of which are used in Chapter 7). Ideally, resting state data is pre-processed in the same manner as event-related fMRI, but the main difference is that events are not extracted from the time-series. Another key difference is session length, an ideal run length for endogenous periods to measure networks usually last at least five minutes, but with the emergence of new analysis approaches, this could change in the future. Furthermore, during acquisition participants can either have their eyes closed or stare at a fixation cross, which is known to show the same robust patterns of activity (Fox et al. 2005). To combat drowsiness, resting state scans in Chapter 7 were all with eyes open rest. However, no direct eye tracking measures or breath/heart rate

measurements were acquired in Chapter 7. Traditionally, the main motivation for resting-state analyses is to investigate connectivity or correlations between endogenous fluctuations in different brain areas. One of the most popular ways of extracting correlated functional networks of activity and also removing correlated artefactual activity elicited by heartbeat, respiration, or head movement is independent component analysis (ICA) (Beckmann et al. 2005). ICA is used as a denoising technique for data in Chapter 7. After the fMRI data is denoised or correlated networks are extracted, different seed regions can be selected and the signal from those regions can be correlated with the rest of the brain. If runs or groups are being compared, then the correlation coefficients can be compared in a GLM (like in Chapter 7). It is also possible to find changes in pre-specified network correlation coefficients with ICA (Beckmann et al. 2005), or changes in the most connected or highest correlated voxels in the brain (Robert W. Cox unpublished observations). Other popular techniques include using graph theoretical techniques (Bullmore & Sporns 2009) to investigate correlation network (or node) strengths and using underlying structural connectivity to inform resting-state functional connectivity (Hagmann et al. 2008). Further resting-state connectivity approaches informed by both models of stochastic dynamics and structural connectivity have also been developed (Deco et al. 2011; Friston et al. 2011).

3.5 Magnetoencephalography

David Cohen in the late 1960s developed magnetoencephalography (MEG) using copper induction coils housed within a magnetically shielded room to detect magnetic activity emanating from the brain. This technique was highly susceptible to noise until the implementation of the superconducting quantum interference device

or SQUID, a type of magnetometer developed by James Zimmerman for MEG (Hansen et al. 2010). Magnetometers can be used to measure extremely weak magnetic fields, such as those induced by neuroelectric activity. The weakness of these signals is an inherent problem with MEG, which warrants surrounding scanners in magnetic shielding.

Unlike fMRI, the neural basis of MEG is well characterised and follows the temporal signature of neural or local field potential (LFP) electrical activity. 1t takes approximately 50,000 active neurons to generate neural activity measurable by MEG, depending on physical configuration (i.e. how dendritic current flows are aligned relative to each other and to the sensors; Murakami & Okada 2006). Both MEG and EEG signals predominantly reflect current flows in the dendrites caused by synaptic transmission (Hansen et al. 2010). Electric dipoles are physically separated charges that create an electric field and are characterised by their position, orientation, and magnitude. Electric current flow generates a magnetic field as can be described by Maxwell's equations. For example, the magnetic flux is clockwise around the direction of current flow (the "right-hand rule") and increases in intensity and radial extent as the current increases.

Although the neurophysiology of MEG and EEG is relatively similar, magnetic (in comparison to electric) fields are less distorted by the skull and scalp. As a result, MEG provides better spatial resolution than EEG. Furthermore, because of the right hand rule, changing current flows perpendicular to the scalp are best detected by EEG, whereas changing current flows parallel to the scalp create changes in magnetic field that are most easily detected by MEG detectors outside the head (Gross et al. 2013).

MEG has been prominently used to study neural oscillations across different frequency bands. Primary frequency bands that have been studied are delta (~1-4 Hz), theta (~4-8 Hz), alpha (~8-12 Hz), beta (~12-30 Hz) and gamma (>30 Hz). In order to analyse oscillatory activity, it is often useful to decompose power across the frequency spectrum (i.e. finding the spectral density or power spectrum) via a Fourier transform of the measured signal. Often it is necessary to examine how this changes over time (i.e. to perform a time-frequency decomposition of power) using a Morlet wavelet transform. To be characterised as an oscillation, activity generally needs to persist for at least 5 to 7 cycles (e.g. a 10 Hz alpha oscillation would therefore need to show activity for at least 500-700 ms for it to be classified as oscillatory in nature). Usually transient increases in power across a wide frequency range are a result of evoked responses that are not oscillatory in nature. In Experiment 1 (Chapter 4), a 5-cycle Morlet wavelet is employed for time-frequency analyses.

3.6 *MEG Source Reconstruction*

Another challenge of MEG is the inverse problem (i.e. the ability to estimate the location, orientation and timecourse of the electric activity within the brain that has caused the changes in magnetic field that are measured outside of the scalp). The development of forward models (i.e. models of the changes in magnetic fields due to specific electrical sources) in recent years has allowed researchers to make estimates about the neural sources of the activity they have measured using MEG (Curio & Nolte 2000), at a relatively course spatial resolution (>5mm). One technique for estimating the sources of oscillatory activity within a particular frequency band is beamforming or spatial filtering. Beamforming is a technique that is used to estimate

the signal arriving from a specified direction in the presence of interference and noise (Van Veen et al. 1998). Implementing the linearly constrained minimum variance (LCMV) beamformer (employed in Experiments 1 and 2), allows researchers to specify a frequency of interest and compare two conditions to determine which potential sources are most likely to have produced the observed change in MEG signal by changing their electrical activity (Barnes & Hillebrand 2003). This estimation of significant activity is accomplished by calculating weights which linearly map sensor data to source locations and then calculating a summary statistic based on the change in oscillatory power between experimental conditions for each voxel. Other types of commonly used beamformer algorithms include synthetic aperture magnetometry (SAM) (Robinson et al. 2004), which is a scalar beamformer that can estimate optimal current direction at each voxel, and dynamic imaging of coherent sources (DICS), which can reconstruct data from one condition rather than a contrast of conditions (Gross et al. 2001).

All of these techniques have been successful in reconstructing sources at cortical surfaces (Gross et al. 2001; Barnes & Hillebrand 2003; Robinson et al. 2004), but reconstruction of deep sources such as the hippocampus has proven controversial (see Quraan et al. 2011). Additionally, system noise is amplified by beamformer weights in a way that increases non-linearly with source depth (Mills et al. 2012) and this is especially true with the LCMV beamformer, where sources tend to be biased towards the middle of the brain and around the cerebellum (unpublished observations). Fortunately, work reconstructing and simulating hippocampal oscillatory sources has been done using an item-context memory task that shows coherent hippocampal theta when measured simultaneously with MEG and intracranially (see supplemental section in Staudigl &Hanslmayr 2013). With further

comparisons between MEG and human intracranial recordings, it should be possible to determine how hippocampal electrophysiological signals are reflected in MEG sensors outside the head.

3.7 *Types of Cross-Frequency Coupling*

Recent studies, including those described in Experiment 2, have investigated the interaction of estimated oscillatory sources in different regions and frequencies. Two oscillations can interact (or show "coupling") in different ways , whether it is power-power coupling (frequency-specific power changes in a specific brain region being correlated with power changes in another brain region), phase-amplitude coupling (modulation of the amplitude of a higher frequency oscillation by the phase of a lower-frequency oscillation) or phase-phase coupling (oscillations that have a consistent phase relationship or alignment, a.k.a. "coherence"); see Figure 6; Jensen & Colgin 2007; Fell & Axmacher 2010). The presence of these types of relationship can be examined to investigate coupling between different oscillations (Canolty et al. 2006; Osipova et al. 2008).

One specific way to measure cross-frequency (phase-amplitude) coupling is the modulation index, which computes the mean amplitude of the higher frequency signal in a set number of low frequency phase bins, and then uses a metric such as the Kullback-Liebler divergence to assess whether this distribution deviates from uniformity (Tort et al. 2010). Another similar way of examining cross frequency coupling (which is used in experiment 2; Chapter 5) is looking at the circular variance (Berens 2009) of the difference between the phase of the low frequency signal and the phase of variation in the amplitude (or "envelope") of the high frequency signal. The less variable the phase differences, the lower the variance, and the higher the 'coupling' or coherence between phase and amplitude. Circular

variance can also be calculated for the phase difference between two signals in the same frequency band to look for phase coherence.

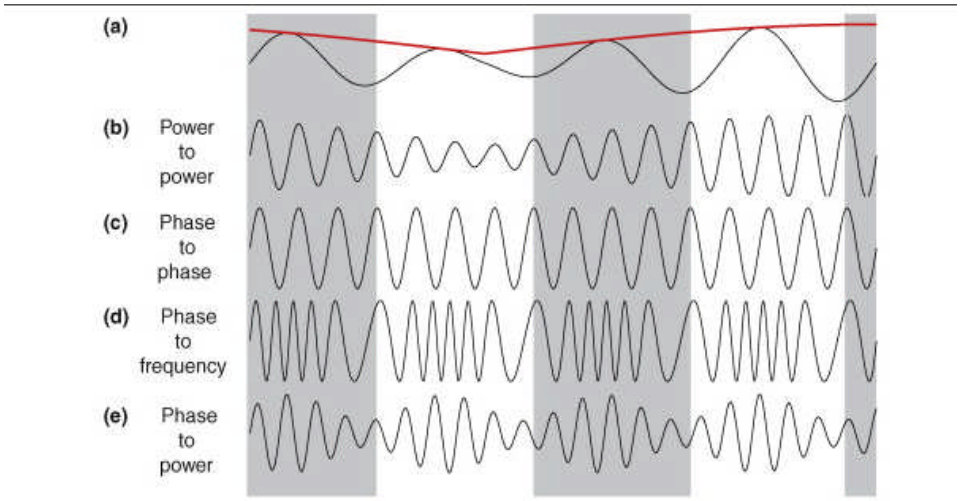

Figure 6: Types of cross-frequency coupling
Taken from Jensen and Colgin (2007) showing examples of different types of phase coupling between the frequency of different neural oscillations. A. 8 Hz theta oscillation with frequency remaining constant, while the power (amplitude in redline) fluctuates over time B. Power of a faster gamma oscillation is correlated with power changes in the theta band oscillations C. Phase-locking between the theta and gamma band oscillations. D. Frequency of gamma oscillation is modulated by the phase of the theta oscillations E. The power of the gamma oscillations is modulated by the phase of theta oscillations, which can also be sometimes observed in phase-amplitude coupling. Notably, these different types of cross-frequency interactions are not mutually exclusive, particularly since power/amplitude changes can bias phase coupling.

Power correlations have also proven to be a fruitful way to investigate resting state activity using MEG source reconstruction (Hipp et al. 2012). The approach used by Hipp et al. (2012), along with other source reconstruction techniques, in investigating resting state activity (Brookes et al. 2011) means the temporal characteristics of endogenous neural fluctuations can be measured non-invasively across the whole brain. This advance holds promise for determining the different oscillatory sources behind the observed patterns of resting state data.

Chapter 4

Experiment 1: Movement-Related Theta Rhythm in Humans:

*Coordinating Self-Directed Hippocampal Learning**

*This chapter derives partly from Kaplan R, Doeller CF, Barnes GR, Litvak V, Duzel E, Bandettini PA, Burgess N (2012) Movement-related theta rhythm in humans: coordinating self-directed hippocampal learning. PLoS Biol 10(2):e1001267

Precis

As outlined in Section 1, the type I movement-related hippocampal theta rhythm has unclear cognitive correlates in rodents. The human hippocampus is commonly associated with mnemonic functions like declarative memory, and how this relates to exploratory hippocampal activity in rodents is undetermined. It is also unclear whether theta rhythm changes related to movement initiation or environmental novelty measured in freely behaving rodents can be measured in humans performing an analogous task. Consequently, in Experiment 1, I had human participants perform virtual navigation tasks in both MEG and fMRI to bridge the gap between hippocampus research on human mnemonic function and rodent spatial exploration.

4.1 Introduction

Spatial exploration provides an ecologically valid experimental paradigm to investigate volitional behaviour and cognition across different species. In freely behaving rodents, the theta rhythm (~4–12 Hz) dominates the hippocampal local field potential (LFP) during translational motion, particularly prominent during initiation of movement (Vanderwolf 1969; O'Keefe & Nadel, 1978; Buzsaki 2002), and has been associated with the encoding and behavioural control of memories (Colgin et al. 2009; Bast et al. 2009). Notably, movement-related theta in rodents is modulated by environmental novelty (Jeewajee et al. 2008) and has shown a correlation between age-related memory decline and decreased amplitude (Tombaugh et al. 2002). However, it has been difficult to disambiguate cognitive influences on the rodent hippocampus from effects of movement *per se* (Kelemen et al. 2005; Shin 2011). In human memory there has been a slightly different

examination of volitional behaviour. The ability to self-initiate memory behaviours was observed as a crucial biomarker for age-related memory decline (Craik 1986 pp. 409-22) and more recently the human hippocampus was observed to be a network hub for the volitional control of memory encoding (Voss et al. 2011). Yet in the electrophysiology domain, human theta research (~4–8 Hz) has mostly focused on passive declarative or working memory (Lisman & Idiart 1995; Klimesch et al. 1996; Tesche et al. 2000; Jensen & Tesche 2002; Fell et al. 2003; reviewed in Duzel et al. 2010). Thus the role of theta in self-directed learning and the correspondence between the role of theta in mnemonic processing and in self-initiated movement is unclear. Some studies have measured hippocampal theta during virtual navigation tasks (Ekstrom et al. 2005; de Araujo et al. 2002; Cornwell et al. 2008; Watrous et al. 2011), and these interactive human tasks may allow assessment of the roles of theta in both self-initiated virtual movement and self-directed learning within the same task.

I helped design a virtual exploration task that parallels foraging paradigms in rodents and behavioural and fMRI studies in humans (Doeller et al. 2008a, 2008b, 2010). In my task, participants used a button box to move and explore a total of six novel or familiar environments (like a video game controller, see Figure 7A), while being scanned by a 275 sensor whole-head Magnetoencephalography (MEG) system. During the learning period of an experimental session, participants were instructed to remember (maintain spatial representations of object location) and navigate to the location of an object (either novel or familiar) in a particular trial. At the beginning of each trial, the participant would be placed in different locations within the environment and then use the button box to freely move around the environment. A single trial consists of navigation towards an object and then running over it, which

marks the end of that trial (Figure 7B; in each session there were six randomized familiar or novel objects each learned over three trials; see Methods for details). After completing the learning phase of a session, participants had a test phase for each object's location. In each test trial, participants were cued with a picture of a previously found object from that session's learning phase. Immediately after being cued, participants were placed in the virtual environment and had to navigate to the location where they had encountered the object and press a button (i.e., “replace” it) to conclude the trial (Figure 7C). As a follow-up (on a later date) with the same participants, I used fMRI functional localizer sessions composed of two analogous learning phases with familiar environments and objects. Participants subsequently completed the test phases outside of the fMRI scanner (refer to Methods for details).

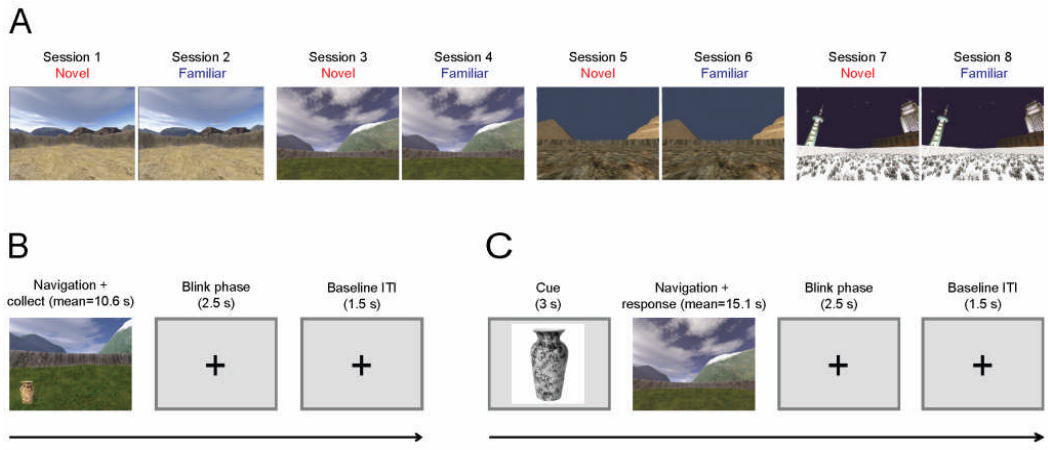

Figure 7. Overview of design and spatial memory task.

(A) Experimental environments shown from the participants' (first-person) perspective. Four different environments are presented in eight experimental sessions. The first two sessions (always the desert environments) provided practice outside of the MEG scanner. Sessions 3–8 contained three novel-familiar environment repetitions with environment order, counterbalanced across participants. (B) Learning phase trial structure. During learning trials, participants use a button box to navigate and “collect” novel and familiar (previously presented) objects (vase shown as example). (C) The test phase, trial structure. After being cued for 3 s with a picture of an object that had been collected in the learning phase of the current

session, participants were placed back in the environment and had to navigate to where they thought the object had been located during that learning period.

To see whether there is a human analogue for the movement-initiation-related theta rhythm found in the rodent hippocampus (type I theta, refer to Vanderwolf 1969), I employed a multi-modal neuroimaging paradigm to look at human memory (Gonsalves et al. 2005). I looked for increased MEG theta power and hippocampal fMRI activity during the onset of self-initiated movement at any point within virtual navigation. To better corroborate movement-related theta, I also investigated the effect of environmental novelty with MEG. Additionally, I tested for relationships between subsequent memory performance and theta power, following related findings in humans (Klimesch et al. 1996; Tesche & Karhu 2000; Sederberg et al. 2003; Osipova et al. 2006; Guderian et al. 2009; Rutishauser et al. 2010; Addante et al. 2011; Fell et al. 2011) and looked to see how this relationship interacted with any movement-related effects. I was interested to see how areas associated with movement- or performance-related theta effects might overlap with the hippocampal-dependent network observed during the active control of learning (Voss et al. 2011). In this way, I aimed to clarify the functional roles of human theta oscillations in cognition and volitional behaviour, and synthesize previous findings in the hippocampus across rodents and humans. Although this experiment does not specifically test for self-directed versus passive learning, my findings suggest that the theta rhythm supports hippocampal-dependent memory by coordinating exploratory movements in the service of self-directed learning.

4.2 Methods

4.2.1 Participants

Twenty right-handed male participants (mean age = 23.5 years, SD = 5.06, range 18–35) gave written consent and were compensated for performing the experimental task, as approved by the local Research Ethics Committee. All participants were right-handed with normal or corrected-to-normal vision and reported to be in good health with no prior history of neurological disease. One participant was excluded from the analysis because of equipment malfunction, and another was excluded from analyses because of signal artefacts. Eighteen right-handed male participants were therefore analysed in the MEG dataset, with one being excluded from the source reconstruction because of a problem with co-registration between the MEG head position and structural MR image. Fourteen of these also participated and were analysed for the fMRI functional localizer.

4.2.2 Virtual Reality Environment

UnrealEngine2 Runtime software (Epic Games) was used to present a first-person perspective viewpoint of four different environments, a dry sandy environment surrounded by dunes (practice environment), a snowy grassy urban environment surrounded by skyscrapers, a rocky desert environment surrounded by pyramids, and a grassy plane surrounded by a circular cliff with a background of mountains, clouds, and the sun. In all environments, background cues were projected at infinity to provide orientation but not location within the arena. Participants moved the viewpoint by using their right hand to press keys to move forward or turn left or right. The viewpoint is ~2 virtual meters above the ground, and all four

environments had the same arena size (area). Virtual heading and locations were recorded every 25 ms.

4.2.3 Stimuli, Task, and Trial Structure

The experiment was composed of eight sessions. The first two sessions were practice sessions using the same virtual desert environment, conducted on a laptop outside the scanner. The participants first familiarized themselves with the environment by navigating around and then collecting objects in the environment by running them over and then being tested on their previous location (Doeller et al. 2008b). These practice sessions lasted for about 2–3 min.

In the MEG scanner, an individual trial consisted of a participant being randomly placed in an environment and having to navigate towards an object to collect and remember its location (average duration ~10.6 s). Participants had three trials to learn the location for each of the six objects. Next, the participants were presented with a grey screen that read “Please Blink” for a 1.5-s blink phase, then a 1-s intertrial baseline where a crosshair was presented on a grey screen. During the learning period of the session, there were 18 trials each consisting of a learning phase blink phase, and baseline intertrial interval (Figure 1). After the learning period of a session was completed, there was a 30-s inter-phase rest period, when instructions on the next phase (test phase) were presented. The test phase for the location of each of the six collected objects started with a 3-s period in which an object was presented on a grey background (cue phase) (Fig. 7). Participants were then randomly placed in the environment and told to navigate to the spot where they believed the pictured object had been located (average duration ~15.1 s). They then pressed a button to “drop” the object or indicate its previous location. Once the

button was pressed a grey screen appeared that read “Please Blink” for a 1.5-s blink phase, followed by a 1-s intertrial baseline.

In the fMRI functional localizer component, participants had functional scans during performance of two different learning period sessions. After they had completed both functional localizer sessions, participants had separate test sessions (i.e., first test for first learning session, second test for second learning session) for each respective learning session to gauge subsequent performance, where they were not scanned. The functional localizer had the same trial structure and amounts as the MEG experiment with the exception of an extended 4-s inter-trial interval (without a blink phase) to account for the timescale of the BOLD signal.

4.2.4 Details of Procedure and Design

Participants were instructed that they were going to navigate through a virtual environment over multiple sessions using a button box, and that they would have to pick up several different objects (six) in the environment, three times each (three objects, three times each for the two practice sessions). The order of trials was randomized but (unknown to participants) separated into three mini-blocks (Doeller et al. 2008b). Object location never changed within a session. After they completed this exploration phase, they were tested at the end in a test period by having to navigate to where they thought the object had been located and press a button.

During MEG scanning, a new environment was presented and then re-presented at the next session as a familiar environment. This occurred on four occasions (three within the MEG), so that half of the eight environments in the experiment were novel and the others were familiar (Figure 7). The order of

environments in the MEG sessions was randomized across participants. Each environment arena had the same distance area, but did have its own unique shape (square, circle, triangle, and rectangle) to differentiate the environment. It is also important to note that virtual movement during navigation trials consisted of continued forward button pressing causing a constant speed of forward motion.

As a control measure for environmental novelty independent of other novelty effects (i.e., object-novelty) during movement initiation, participants were presented with counterbalanced familiar or novel objects within each environment. Following the practice sessions, the objects presented in an environment were comprised of objects that the participants had either collected ("familiar") or not collected ("novel") in a previous session. Familiar objects were first introduced during the practice session outside of the scanner.

For the fMRI functional localizer, there was no manipulation of environmental or object novelty. The two sessions were conducted in the circle mountain environment used in the MEG experiment with all novel objects for both sessions. Otherwise, the procedure was analogous to the MEG design.

4.2.5 MEG Acquisition

Recordings were made in a magnetically shielded room with a 275-channel Canadian Thin Films (CTF) system with superconducting quantum interference device (SQUID)-based axial gradiometers (VSM MedTech Ltd.) and second-order gradients. Neuromagnetic signals were digitized continuously at a sampling rate of 480 Hz and behavioural responses were made via an MEG-compatible response pad. I used a high pass filter of 0.1 Hz and a low pass filter of 120 Hz. Head positioning

coils were attached to nasion, left, and right auricular sites to provide anatomical coregistration. Coils were energized before and after each session to determine head movement and position within the MEG dewar. At acquisition for some participants, some sensors were corrupted. As a result, only 270 of the 275 sensors were analyzed to keep data consistent across all participants.

4.2.6 MEG Data Analysis

Data were analyzed with SPM8 (Wellcome Trust Centre for Neuroimaging, London) (Litvak et al. 2011) and FieldTrip toolbox (Donders Centre for Cognitive Neuroimaging, Nijmegen, the Netherlands) (Oostenveld et al. 2011) within MATLAB 7 (The MathWorks).

4.2.6.1 Pre-Processing

Although the total trial duration varied, to assess the effects of virtual movement and novelty, we defined fixed-length segments where the participant's state was comparable across trials at any period (learning and test) in the experiment. Epochs corresponding to movement initiation were defined as −200 to 800 ms relative to the initiation of forward displacement at any point in any navigation (learning and test periods) trial, where participants moved for at least 1,000 ms. As an equal length comparison condition within the experiment, stationary epochs were characterized as 500 ms after a participant had stopped moving for a duration of 1,000 ms without any forward displacement at any point during any navigation (learning and test periods) trial. Both of these windows were extended by an additional 1,000 ms on either side for analysis purposes. Importantly, participants' top speed remained constant during all movement periods. Within the movement-

based analyses, epochs were defined as belonging to one of ten different conditions in which movement and stationary epochs were separated by whether they occurred within novel environments or during novel object trials: movement onset during a familiar object trial, movement onset during a novel object learning trial, stationary period during a familiar object learning trial, stationary period during a novel object learning trial, and the 1,000 ms inter-trial baseline condition. To look at environmental novelty, these five conditions were also defined the same way, but the extra factor of session environment (familiar or novel) was added.

For the subsequent memory analysis during exploration (1-s movement and stationary epochs), the epochs were divided into well-performed trials and poorly performed trials at a median split for each participant. In this analysis there were five trial types: movement onset during a well-performed trial, stationary period during a well-performed trial, movement onset during a poorly performed trial, stationary period during a poorly performed trial, and the inter-trial baseline.

On average each participant had 178.2 movement onset epochs versus 197.8 stationary epochs with 138 baseline epochs. For the environmental novelty contrast, each participant had on average 90.7 virtual movement initiation epochs in a novel environment, 87.5 virtual movement onset epochs in a familiar environment, 105.1 stationary epochs in a novel environment, 92.7 stationary epochs in a familiar environment, 69 baseline epochs in a familiar environment, and 69 baseline epochs in a novel environment. For object novelty, each participant had an average of 85.2 virtual movement onset epochs measured during novel object trials, 93 virtual movement onset epochs measured during familiar object learning trials, 98.3 stationary trials measured during novel object trials, and 99.5 stationary trials

measure during familiar object trials. For the subsequent memory analysis during navigation (an average total of 273.1 epochs per participant), there were 62.9 virtual movement onset epochs during subsequent accurately performed learning trials, 62.9 virtual movement onset epochs during subsequent inaccurately performed learning trials, 73.3 stationary epochs during subsequent accurately performed learning trials, 73.9 stationary inaccurately performed learning trials, and 102 baseline trials.

For the cue period analysis, the 36 3-s-long cue periods were divided into well-performed trials versus poorly performed trials. There was also a 1-s baseline prior to each 3-s-long cue period trial.

4.2.6.2 Time-Frequency Analysis

Two seconds of padding (one second at each end) were added to the movement epochs to capture more theta cycles. Additionally, trials were inspected and removed if they contained eyeblink artifacts. Data were downsampled to 120 Hz, and a five-cycle morlet wavelet time-frequency analysis ranging from 3 to 48 Hz with a frequency resolution of 1 Hz was conducted. Lower delta frequencies (below 3 Hz) were not measured because of the limited number of possible cycles in the short trial length and edge effects. The same analysis stream was followed for the cue phase analysis, with the exception that cue epochs lasted 3 s with another 1 s pre-stimulus baseline, in which the participant was intended to stare at a fixation cross. With 3-s-long epochs there was a lower chance of edge effects in the delta frequency band (1–4 Hz), so I extended our time-frequency analysis to 2 to 48 Hz. Still, to avoid edge effects, the 3-s-long time window was reduced to 2.5 s.

Next, a weighted average (i.e., making sure that trial numbers between participants were weighted into calculated averages) of time-frequency trials was calculated within participants and session by condition. Data were then log transformed and baseline corrected (i.e., the data were expressed as a multiple of baseline power). For the movement analyses, the baseline was computed from a set of 1,000 ms baseline trials. For the cue period analysis the first 1,000 ms prior to the cue onset were used as a baseline.

Time-frequency data were then converted into Neuroimaging Informatics Technology Initiative (NIfTI) format. This produced a 3-D image of Channel Space×Time. The frequency dimension was averaged across the theta frequency band (4–8 Hz) based on our a priori hypotheses.

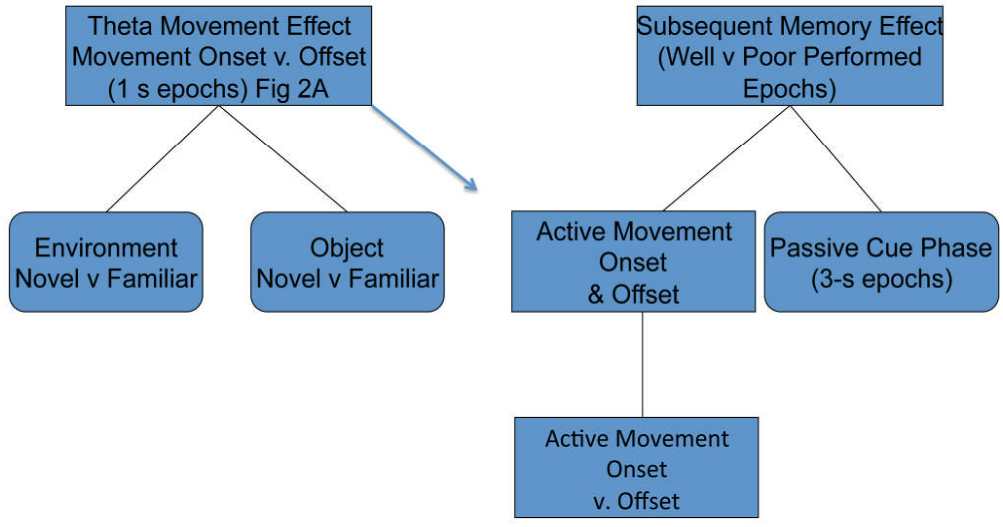

Figure 8: MEG analysis flow chart

A flow chart of the MEG time-frequency data analysis stream.

4.2.6.3 MEG Statistical Analysis

For the virtual movement effect, a paired *t* test of virtual movement onset and offset conditions was conducted with a Family Wise Error (FWE) corrected cluster threshold of $p<.05$, because of our previous event-related hypothesis to the effect and time scale of theta during movement initiation (Litvak et al. 2011). For object and environmental novelty movement effects, a one-way ANOVA for the 2×2 factors of object novelty versus environmental novelty was used. The same statistical threshold as for the virtual movement effect was also used. The (cue phase and subsequent memory) performance effects were calculated with a paired *t* test with a threshold of $p<.001$ uncorrected without the cluster correction because of our strong a priori hypothesis from the past literature looking at theta and memory performance and the lack of a specific event-related hypothesis for the time-scale of power changes (Duzel et al. 2010).

4.2.6.4 MEG Source Reconstruction

The linearly constrained minimum variance scalar beamformer spatial filter algorithm (Sekihara et al. 2004) from SPM8 was used to generate source activity maps in a 10 mm grid. Coregistration to the MNI coordinates was based on three fiducial points: nasion and left and right preauricular. The forward model was derived from a single-shell model (Nolte & Curio 2000) fit to inner skull surface of the inverse normalized SPM template. The beamformer source reconstruction is based on two stages (Barnes & Hillebrand 2003). First, based on the data covariance and lead field structure, weights are calculated which linearly map sensor data to each source location. Second, a summary statistic based on the change in source power or amplitude over experimental conditions is calculated at each voxel. In this

case the summary statistic at each voxel is the change in source power in the 4–8 Hz band normalized by the projected sensor white noise power. In this case, the periods under comparison were accurately and inaccurately remembered trials in a time window 500–1,500 ms after Cue onset (i.e., within the cue period). For each participant these summary statistic images were entered into a second-level one-sample *t* test in SPM8. A statistical threshold of $p<.001$ was used.

The beamformer source extraction for the movement initiation effect was measured from two locations (medial prefrontal cortex, x = 10; y = 30; z = 22; right anterior hippocampus, x = 24; y = −6; z = −18) and projected through a spatial filter constructed from the covariance matrix comprising 1-s Navigation conditions with 1-s of padding on either side for three conditions: movement, stillness, and pre-navigation baseline. Subsequently, the same time-frequency wavelet analysis from the sensor-level analyses was run on these two virtual sensor locations from the mPFC and hippocampus.

4.2.7.1 fMRI Acquisition

Functional images were acquired on a 3T Siemens Allegra scanner. Blood oxygenation level dependent (BOLD) T2*-weighted functional images were acquired using a gradient-echo EPI pulse sequence acquired obliquely at −45 degrees with the following parameters: repetition time, 2,880 ms; echo time, 30 ms; flip angle, 90 degrees; slice thickness, 2 mm; interslice gap, 1 mm; in-plane resolution, 3×3 mm; field of view, 64×72 mm^2; 48 slices per volume. A field-map using a double echo FLASH sequence was recorded for distortion correction of the acquired EPI (Weiskopf et al., 2006). After the functional scans, a T1-weighted 3-D MDEFT

structural image (1 mm^3 resolution) was acquired to co-register and display the functional data.

4.2.7.2 fMRI Preprocessing

All preprocessing and analyses were performed with SPM8 (www.fil.ion.ucl.ac.uk/spm). All individual structural images underwent segmentation (into grey matter, white matter, and cerebro-spinal fluid), bias correction, and spatial normalization to the MNI template using "unified segmentation" (Ashburner & Friston, 2005). Using the Montreal Neurological Institute (MNI) template brain, the first six EPI volumes were discarded to allow for T1 equilibration. EPI images had distortion correction and were realigned spatially to the time series' first image based on the collected field map (Hutton et al., 2002) and the interaction of motion and distortion using the Unwarp routines in SPM (Andersson et al. 2001; Ashburner & Friston 2005). Functional images were normalized based on the spatial parameters derived from the normalization of their structural images. Normalized EPI images were spatially smoothed with an 8 mm isotropic FWHM Gaussian kernel. Data were high pass filtered at 128 s. All coordinates are in MNI space.

4.2.7.3 fMRI Data Analysis

Statistical analyses were performed using a univariate general linear model (GLM) with a rapid event-related experimental design. There were two 1-s conditions of interest that were the same as the MEG, movement onset (initiation) and movement offset (no movement) conditions, which were modelled as a boxcar function (duration of 1 s) and convolved with the canonical hemodynamic response

function (HRF) to create regressors of interest. Participant-specific beta values (parameter estimates) were calculated for each voxel, and the respective contrast images (movement onset versus offset) were entered into one-sample *t* tests in a second-level random-effects analysis. In a second analysis across participants, the movement onset versus offset contrast images were correlated with each participants' mean object replacement performance (mean distance error in virtual meters) during the test phase. Based on our strong a priori hypothesis about the hippocampus, we chose the threshold of $p<.001$ (uncorrected for multiple comparisons) with an extent threshold of 5 voxels.

4.3 Results

4.3.1 Behavioural Results

The average lengths of navigation trials in the learning and test periods were 10.6 s and 15.1 s, respectively (averaged over the 20 participants measured). Participants displayed a linear trend of spending less time navigating during learning ($p = .006$, $F(1, 19) = 9.416$) and test ($p = .015$, $F(1, 19) = 7.105$) trials in later experimental sessions. Replacement error (the distance between indicated object location and the correct location within the environment during the test phase) showed a linear trend of decreasing object replacement distance over the whole experiment (i.e., improving performance, $p = .027$, $F(1, 19) = 5.84$), but no significant change in error within any individual session ($p = .141$, $F(6, 19) = 1.707$, see Figure S1). There was no significant difference in replacement error between new and familiar environments ($p = .141$, $t(19) = -1.535$), but performance for novel

objects was significantly better than for familiar objects (p = .023, $t(19)$ = 2.464). The better memory performance for novel objects was not surprising, since familiar objects were used in a different location in a previous environment, which could lead to source interference.

4.3.2 Time-Frequency Analyses

4.3.3 Movement initiation analyses

In order to perform an event-related characterization of the data, we analysed 1-s periods of movement onset or being stationary within any point of a navigation trial using five-cycle Morlet wavelets (see Figure S2; refer to Materials and Methods for details). We refer to 1-s periods of movement onset (initiation) and stationary periods during navigation as "epochs." These 1-s time periods were used in MEG analysis during navigation across participants (n = 18) for the movement onset analysis. I used paired t tests to compare power during different types of epochs over multiple trials, where we looked for theta effects averaged across all sensors. Here and in the novelty analysis below I used a significance threshold of p<.05 Family Wise Error (FWE) cluster corrected for multiple comparisons (over time and frequency) for both the movement and novelty effects (Litvak et al. 2011). There was a significant difference in theta power (i.e., 4–8 Hz power averaged over all sensors) for movement onset compared to stationary epochs, that peaked at ~−50 ms (cluster-level FWE corrected p<.040, $t(17)$ = 5.07) before the onset of movement (Figure 9A–B). This demonstrated a significant increase in transient-induced theta power (centered around ~5 Hz) preceding a 20 Hz (beta frequency) button press-related power increase. In both traces at the sensor level, the oscillatory nature of these differences is apparent (see Figure 13 for an example). There was also activity

at 14–16 Hz approximately 200 ms before movement, concurrent with an extension of the theta cluster. The oscillatory and temporal topography of the beta and theta oscillations on the time frequency plot (see Figure 9) parallels previous findings separating movement-related power changes during spatial wayfinding from simple motor planning during navigation experiments (Caplan et al. 2003).

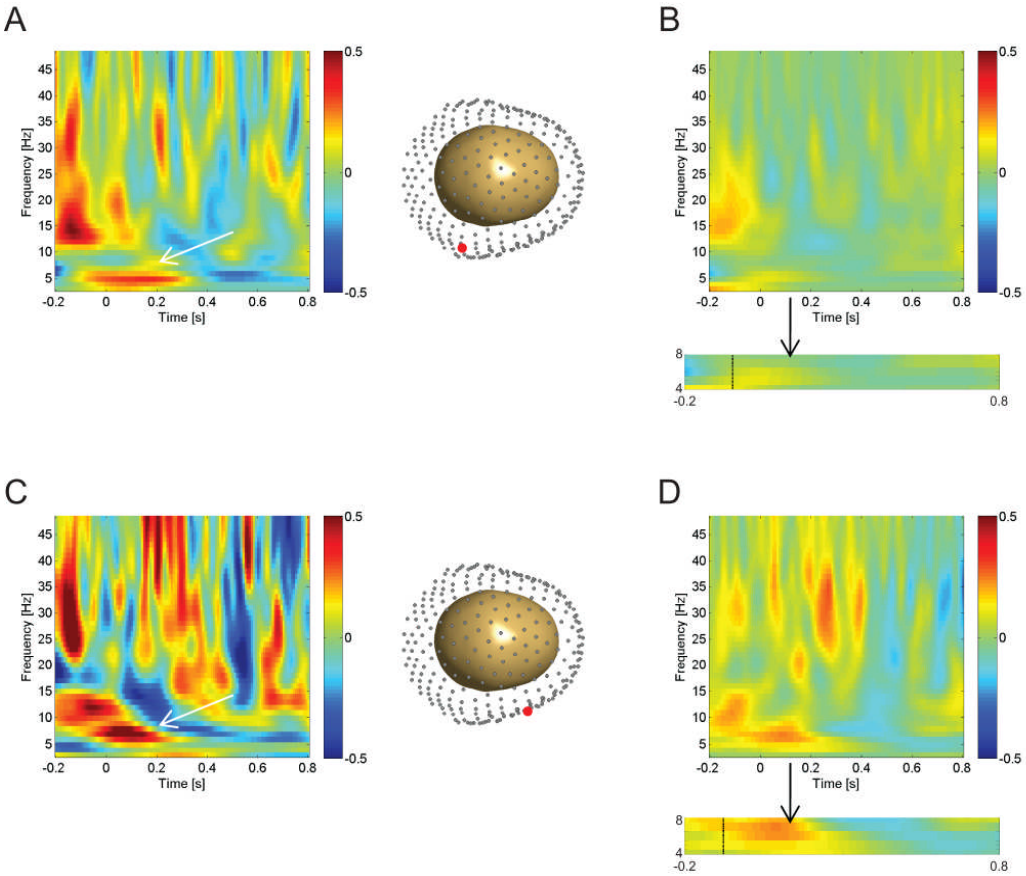

Figure 9: Movement-related MEG time-frequency effects.

Plots show MEG signal as baseline corrected log normalized difference scores (dB, z axis) against time (*x*-axis, seconds) and frequency (*y*-axis, Hz), averaged across participants (n = 18). (A) The effect of movement initiation during navigation (left panel) at an exemplary single sensor of interest, MRT16, whose posterior right middle temporal location is highlighted in red in a 3-D representation of the MEG sensors around the head (right panel). (B) The effect of movement initiation averaged across all 270 MEG sensors (top). Box below highlights the theta band (4–8 Hz), the vertical line (~−50 ms) signifies the start of the significant temporal cluster within the theta band (FWE p<.05). (C) The effect of environmental familiarity on the movement initiation effect (movement initiation in a familiar environment versus movement initiation in a novel environment) at an exemplary single sensor of interest, MRF56 (left), whose middle right frontal location is highlighted in red (right). (D) The effect of environmental familiarity on the

movement initiation effect averaged across all 270 MEG sensors. Box below (format as Figure 2B) shows effect at ~−83 ms within the theta band (FWE p<.05).

4.3.4 Novelty analyses.

I also tested the persistence of movement initiation effects by comparing the effect with regards to environmental and object novelty. A 2×2 ANOVA with factors of environmental and object novelty was performed on the time-frequency signal from all sensors for movement onset versus stationary epochs. Increased theta power was found for familiar versus novel environments during the initiation of movement, with the peak increase beginning at −83 ms (cluster-level FWE p<.048, $t(17) = 4.15$). However, no theta power increases were observed for the reverse contrast (novel versus familiar environments) or any effects due to the contrast between object novelty versus familiarity (Figure 9C–D). The increased theta power related to movement initiation in familiar versus novel environments resembled that for the movement onset effect alone, but was stronger and covered a wider range of frequencies within the theta band.

4.3.5 Performance Effects

In a next step, I looked at subsequent memory effects in the passive pre-navigation planning or cue period (where participants were presented with a picture of a previously collected object) prior to active retrieval by comparing a median split of trials (within participants) corresponding to subsequently accurately versus inaccurately replaced objects. I had a strong a priori hypothesis of increased theta for performance, so I set my significance threshold at p<.001 uncorrected. Using a paired t test across participants, I found a significant subsequent memory-related theta power increase in the average signal of all sensors during the cue phase, peaked

at 583 ms (p<.001 uncorrected, $t(17) = 4.38$). Induced theta oscillations were clearly visible for most of the epoch (Figure 10A–B). There was also a significant correlation (Pearson value: $p = .027$; $r = -.519$; Spearman value: $p = .023$; $r = -.534$; $df(17)$) between each participant's peak theta power from this contrast with their average distance error.

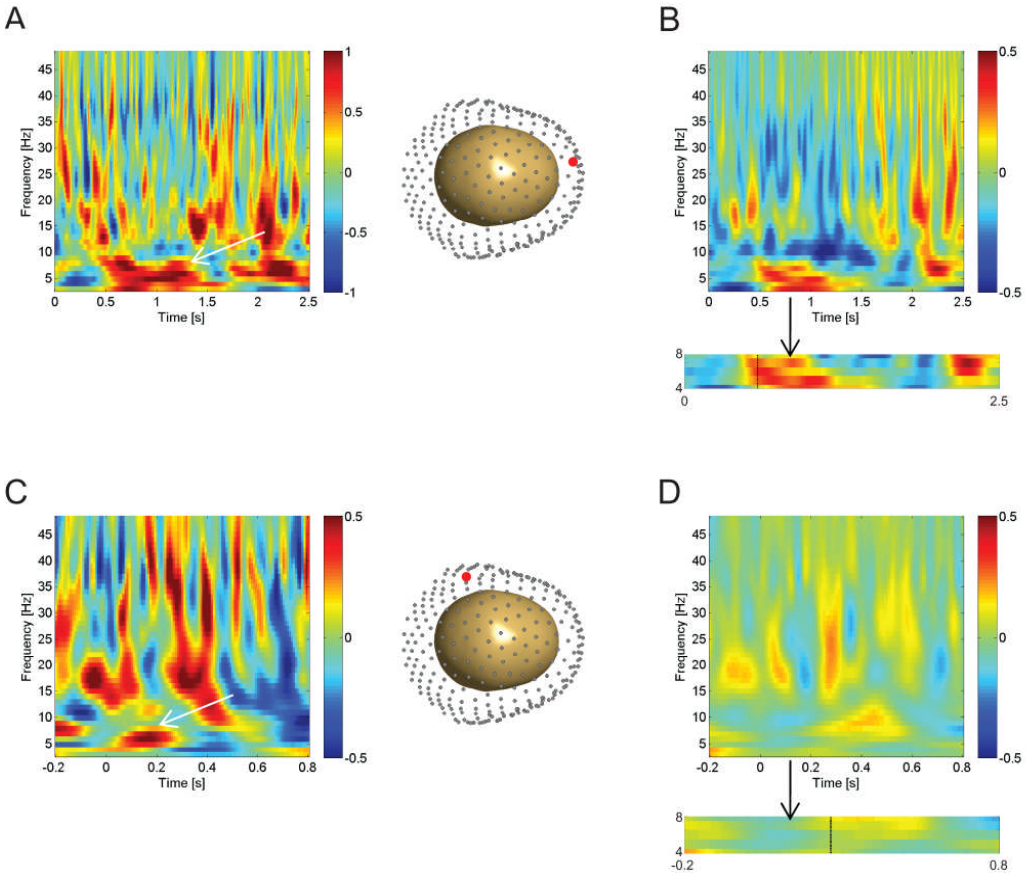

Figure 10: Performance-related MEG time-frequency effects.

Subsequent performance effects are shown as the difference between time-frequency spectra for accurate trials versus inaccurate trials. Trials were divided into accurate and inaccurate according to whether replacement accuracy for that trial was above or below the participant's median accuracy across all trials. (A) The effect of subsequent performance during the cue period, shown at an exemplary single sensor of interest, MLF51, whose middle left frontal location of the singe sensor is highlighted in red (right). (B) The effect of subsequent performance during the cue period averaged across all 270 MEG sensors. Box below highlights significant temporal cluster (~583 ms) within the theta band (p<.001; format as in Figure 2). (C) The interaction of movement initiation and subsequent performance effects (i.e., the difference between the movement-initiation effects in accurate versus inaccurate trials), shown at an exemplary single sensor of interest, MLT15, whose posterior left

middle temporal location is highlighted in red (right). (D) The interaction of movement initiation and subsequent performance effects averaged across all 270 MEG sensors. Box below highlights a significant temporal cluster (~283 ms) within the theta band (p<.001; format as in Figure 9).

I also combined all movement onset and stationary epochs during the learning phase and ran a paired t test, dividing the trials based on the median split within participants according to subsequent performance on the object encountered during that trial. A significant theta effect was found for accurate versus inaccurate subsequent performance, peaked at 367 ms (p<.001 uncorrected, $t(17) = 4.04$). To distinguish whether the movement onset or stationary epochs contributed more to this effect, I tested for an interaction between movement onset or stationary epochs and subsequently well-performed versus poorly performed trials from the movement initiation analysis. The subsequent performance-related difference in theta power was greater for movement onset than stationary epochs (p<.001 uncorrected, peak at ~283 ms; $t(17) = 3.67$; Figure 10C–D). No subsequent performance-related theta power increases were seen during stationary compared to movement onset epochs. Finally, there also appeared to be a significant increase in (~9–12 Hz) alpha oscillatory power corresponding to movement onset in high-performing trials (Figure 10D). Recent work has shown theta and alpha oscillations in the hippocampus and perirhinal cortex are related to successful subsequent memory performance (Fell et al. 2011).

4.3.6 fMRI Analyses

Within our multi-modal neuroimaging approach, I ran follow-up fMRI analyses to corroborate my MEG results. I ran a one-sample t test on the contrast images for 1-s movement initiation periods versus stationary periods, at any point during virtual navigation within the two learning sessions, for the 14 participants

who underwent fMRI scanning, using the uncorrected threshold of $p<.001$, $t(13) = 3.85$, for all contrasts. Using a whole brain univariate GLM I found the right hippocampus to be significantly more active for movement onset than stationary epochs (peak voxel: x = 24, y = −6, z = −18, Z-score = 3.83; see Figure 11A). I also observed activations in the bilateral cerebellum, inferior frontal gyrus, inferior parietal lobule, and basal ganglia (Table 1). In the reverse contrast, we saw increased bilateral posterior parahippocampal cortex activation for stationary periods compared to movement initiation (right peak: x = 18, y = −44, z = −10; Z-score = 4.38; left peak: x = −20, y = −54, z = −6, Z-score = 4.14). Thus, there is a transition from parahippocampal activation during stationary scene processing to hippocampal activation during movement initiation.

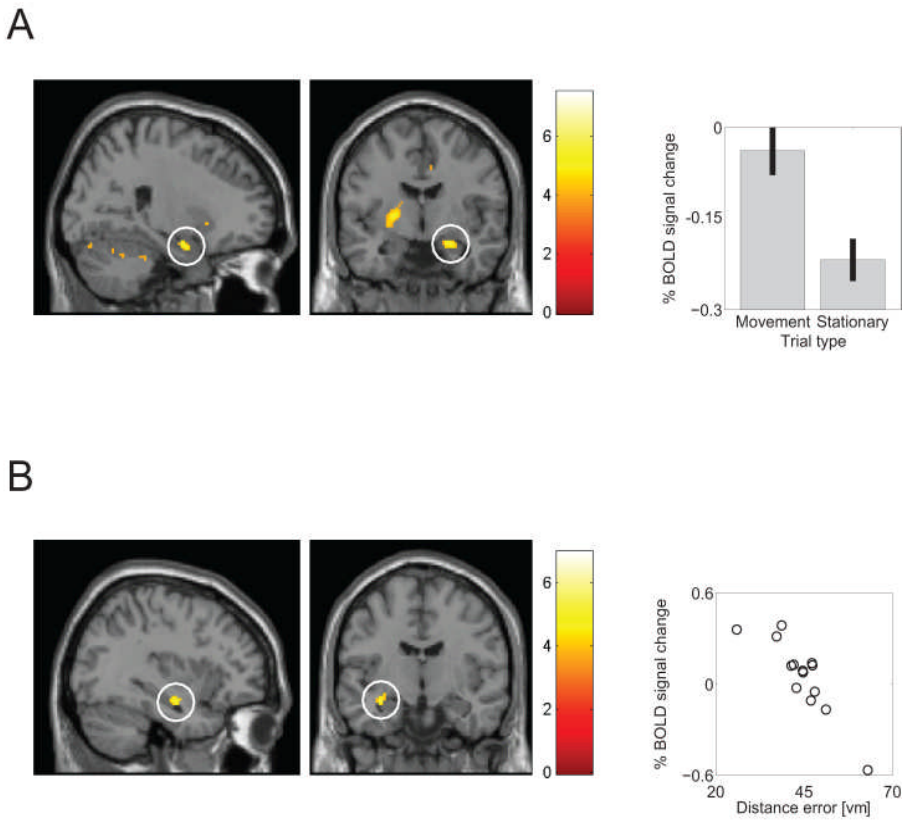

Figure 11: Movement- and performance-related fMRI effects.

(A) Left: Sagittal and coronal slices showing right hippocampal activation for movement initiation compared to stationary periods (peak x = 24; y = −6; z = −18; Z-score = 3.83, thresholded at $p<.001$). Right: Percent signal change at right hippocampal peak-voxel averaged across 14 participants for movement and stationary periods (mean± SEM). (B) Left: Sagittal and coronal slices showing the correlation of left hippocampal activation during movement initiation with each participant's mean performance (peak voxel x = −32; y = −10; z = −14; Z-score = 3.66; thresholded at $p<.001$; right-hippocampal activation, not shown, has peak x = 40; y = −18; z = −14; Z-score = 3.20). Right: Percent signal change in left hippocampus for each participant plotted against his or her average replacement accuracy in virtual meters. Activations are overlaid on the SPM8 canonical single-participant T1 image.

To follow up the movement-initiation finding, I correlated each participant's average subsequent accuracy (mean distance error) with the movement initiation fMRI effect (movement versus stationary contrast images). I found increased hippocampal activity associated with better performance (left peak: x = −32, y = −10, z = −14; Z-score = 3.66; right peak: x = 40, y = −18, z = −14; Z-score = 3.20, see Figure 11). Increased precuneus, bilateral inferior parietal lobule, ventral occipitotemporal area, and bilateral basal ganglia activity was also seen in this contrast (Table 2). No voxels showing increased activation for worse performance survived my threshold.

Region	***x***	***y***	***z***	**Z-score**
L Cerebellum	-34	-48	-32	4.59
R Cerebellum	30	-40	-28	3.95
R Superior Parietal Lobule	16	-78	48	4.49
L Striatum	-22	-8	6	4.06
R Striatum	26	14	-2	3.58
Cingulate Gyrus	-4	-22	42	3.98
R Inferior Frontal	56	26	2	3.97

Gyrus				
L Inferior Frontal Gyrus	-60	8	26	3.33
R Hippocampus	24	-6	-18	3.83
R Insula	44	12	-8	3.76
Midbrain	10	-24	-26	3.76
R Lateral Occipital Area	36	-84	-6	3.64
L Lateral Occipital Area	-48	-62	-2	3.60
R Caudate	16	4	14	3.30
L Inferior Parietal Lobule	-30	-46	64	3.21

Table 1. Significant fMRI activations for the movement initiation contrast, at the p<.001 uncorrected threshold.

Region	***x***	***y***	***z***	**Z-score**
Retrosplenial Cortex	-6	-44	0	4.33
R Ventral Occipitotemporal Cortex	56	-54	-4	3.93
R Inferior Parietal Lobule	66	-34	20	3.92
L Inferior Parietal Lobule	-56	-68	8	3.60
L Hippocampus	-34	-10	-16	3.66
R Hippocampus	40	-18	-12	3.20
L Globus Pallidus	-8	10	-6	3.49
R Middle Temporal Gyrus	56	-16	-16	3.48

L Middle Temporal Gyrus	-42	-66	6	3.47
R Caudate	12	8	2	3.37
L Secondary Visual Cortex	-12	-86	24	3.22

Table 2. Significant fMRI activations for the movement initiation contrast correlated with each participant's replacement performance (overall distance error), at the $p<.001$ uncorrected threshold

4.3.7 Theta Source Analyses

I estimated anatomical sources for the 3-s Cue Period Subsequent Performance contrast image using a Linearly Constrained Minimum Variance (LCMV) beamformer algorithm (Sekihara et al., 2004) implemented in SPM8. I looked for theta (4–8 Hz) sources across the whole brain within the 500–1,500-ms theta effect time window (Figure 10B), at the uncorrected significance threshold of $p<.001$, $t(16) = 3.686$, for all contrasts. I found two significant peaks in the right posterior hippocampus (x = 18; y = −36; z = 4; Z-score = 3.26; x = 26; y = −50; z = 4; Z-score = 3.19, see Figure 12) and none elsewhere in the brain. I also conducted the same analysis on the 1-s Movement Initiation effects but saw no significant effects, possibly because of the transient (<500 ms) nature of the theta power change. I also used beamformer analyses to estimate the signal from the hippocampal coordinates of our fMRI movement initiation effect (MNI coordinates: x = 24, y = −6, z = −18) and a frontal midline region (MRI coordinates: x = 10; y = 30; z = 22). I observed strong theta increases (centered around ~4 Hz) in the hippocampus and in the medial Prefrontal Cortex (centered around ~6 Hz) during virtual movement initiation versus stationary trials (Figure 14).

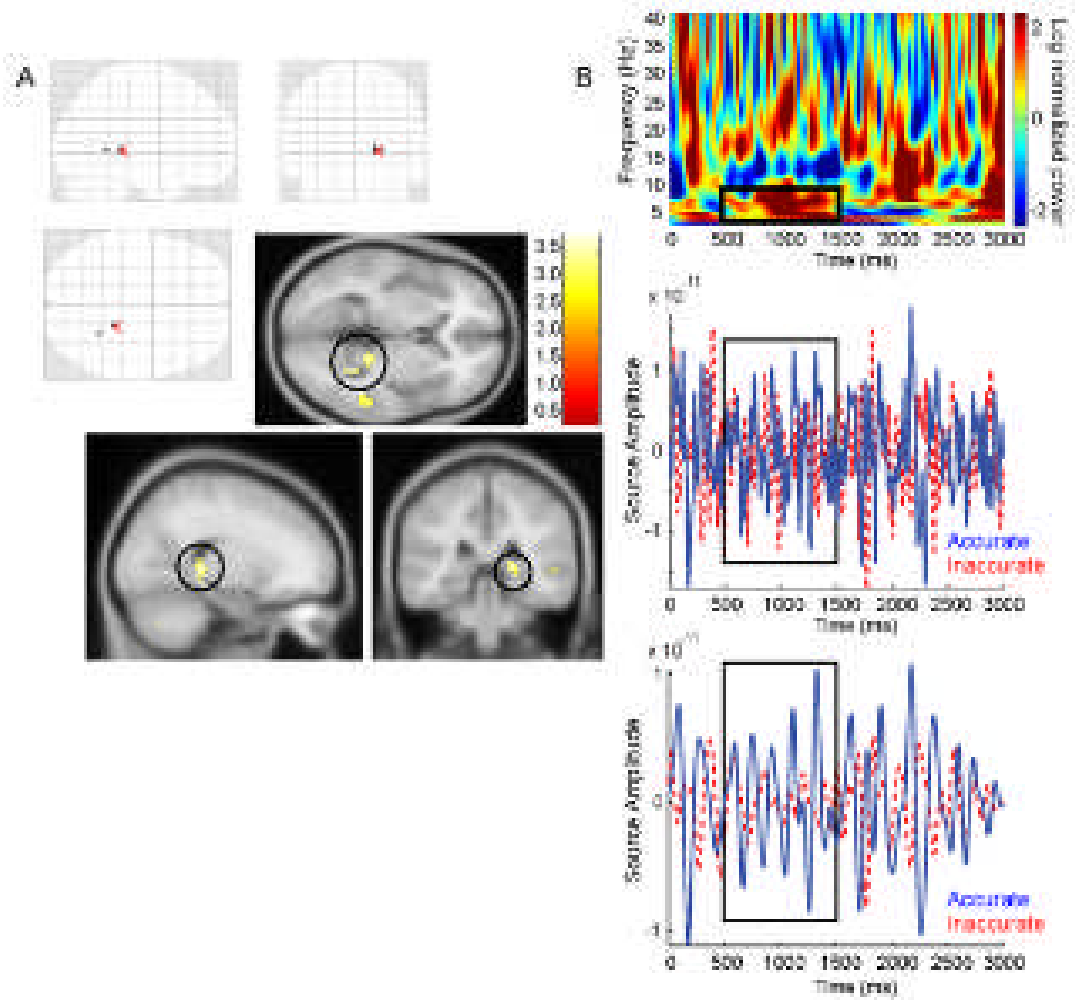

Figure 12: MEG source reconstruction

(A) Top: "Glass brain" showing performance-related posterior right hippocampal source in the 4–8 Hz theta band from 500–1,500 ms within the 3-s Cue Period, which were the only significant sources of theta in the whole brain (peak-voxels: x = 18; y = −36; z = 4; Z-score = 3.26, highlighted by red arrows and x = 26, y = −50, z = 4; Z-score = 3.19, thresholded at $p<.001$, see Figure 3A–B for corresponding sensor-level plots). Bottom: Hippocampal sources shown overlaid on the SPM8 canonical average MNI 152 T1 image, significance threshold at $p<.005$ for display purposes. (B) Top: Single participant spectra from beamformer source extraction of a virtual sensor in right posterior hippocampus (x = 18; y = −36; z = 4). The black box shows the window used for the LCMV beamformer (500–1,500 ms; 4–8 Hz). Middle: Representative traces from the same participant and site for accurate trials (blue) and inaccurate trials (red). Bottom: Filtered versions of the traces (3.5–8 Hz). Source Amplitude and Power for these source extractions are measured in Ampere Meters.

4.4 Discussion

I sought to investigate volitional movement-related theta oscillations in and their relation to self-directed memory encoding and hippocampal fMRI activity during an ecologically valid virtual spatial memory task using MEG. I found increased theta power during movement initiation (Figure 9A–B), an effect that was enhanced in familiar environments (Figure 9C–D). Additionally, I found performance-related theta power increases during navigation, which were stronger during volitional movement initiation than stationary periods (Figure 10C–D). I also observed theta power increases (Figure 10A–B) that were localized to the right hippocampus (Figure 12) during the static cue phase, where increases predicted subsequent spatial memory performance. fMRI functional localization of movement initiation periods revealed increased hippocampal activity (Figure 11A), and fMRI activations related to subsequent memory performance were also seen in the hippocampus during self-initiated movement (Figure 11B).

The increase in theta power at the initiation of volitional movement parallels the increased theta power seen in rodent hippocampus during the initiation of movement (Vanderwolf, 1969; O'Keefe & Nadel 1978) and the dominant influence of motoric contributions versus cognitive factors in rodent studies of theta (Kelemen et al. 2005; Shin, 2011). These findings corroborate previous findings of virtual movement-related theta oscillations in humans (Caplan et al. 2003; Ekstrom et al. 2005; Jacobs et al. 2010) and rodents (Harvey et al. 2009). In my task, the top movement speed was held constant, but there has been evidence that delta/theta power in the human hippocampus increases with virtual movement speed during navigation (Watrous et al. 2011). The increase in theta power in familiar environments compared to novel ones during the initiation of movement parallels the

reduction in theta frequency (but not necessarily power) found when a rat enters a novel environment (Jeewajee et al. 2008). These changes were only found in response to environmental familiarity versus novelty, but not object familiarity versus novelty, supporting my hypothesis of theta power changes specifically in response to environmental novelty. This is consistent with the rodent literature where processing the novelty of the environment, rather than the objects within it, is specifically dependent on the hippocampus (Save et al. 1992a,b; Lee et al. 2005).

In addition to motoric and environmental factors, I also found links between theta power and cognitive performance, following previous studies in humans. Theta power in the (static) cue period (where participants coordinated the retrieval of object location prior to navigation) reflected subsequent replacement accuracy, consistent with previous MEG and EEG studies of human memory (Klimesch et al. 1996; Sederberg et al. 2003; Osipova et al. 2006; Guderian et al. 2009; Rutishauser et al. 2010; Addante et al. 2011; Fell et al. 2011). The source of this theta effect was localized to the right hippocampus, in line with previous work (Doeller et al. 2008b; Abrahams et al. 1997; Bohbot et al. 1998; Spiers et al. 2001; Burgess et al. 2002). Notably, sensor-level peak theta power was higher in better performing participants, suggesting behavioural relevance.

I next examined the relationship between the movement-initiation-related theta during learning trials and subsequent performance in test trials. I found that the theta power difference between movement-initiation and stationary periods increased in trials in which there was more accurate subsequent memory performance.

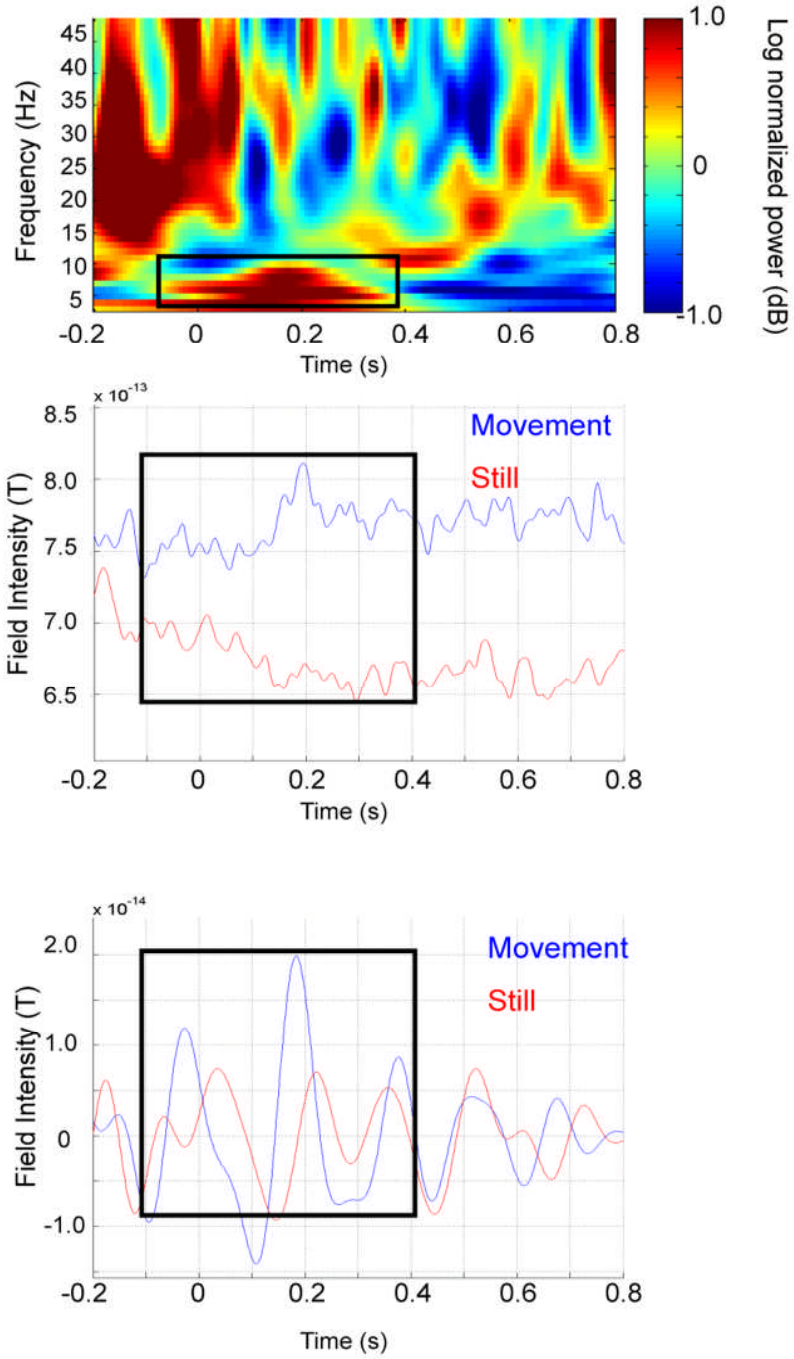

Figure 13: Virtual movement initiation traces

Top: Single participant movement initiation spectral theta effect from same single Sensor (MRT16) shown in Figure 9A. Middle: Representative individual traces from sensor MRT16 showing the difference in the same time window between movement (blue) and still (red) periods in the same single subject. Bottom: Filtered (3–10 Hz) individual trace difference in theta oscillatory activity during movement initiation (blue) and stillness (red). Field intensity for all traces in Tesla.

Analysis of 1-s movement initiation periods with my fMRI functional

localizer task demonstrated increased activity in the right hippocampus, in line with

previous studies linking the right hippocampus to navigation (Abrahams et al. 1997; Bohbot et al. 1998; Spiers et al. 2001; Burgess et al. 2002; Doeller et al., 2008b). My movement initiation fMRI contrast showed an overlap with a hippocampal-centred network including the cerebellum, lateral frontal areas, and IPL (inferior parietal lobule) concerned with the active encoding of item locations (Voss et al. 2011). Notably, the main structures active during my movement initiation fMRI localizer, the basal ganglia and the cerebellum, show theta oscillatory synchronisation to the hippocampus during learning in small mammals (Berke et al. 2004; DeCouteau et al. 2007; Hoffmann & Berry 2009), and functional connectivity has been observed between hippocampus and cerebellum (Habas et al. 2009; Krienen et al. 2009; Voss et al. 2011) and basal ganglia (Mattfield & Stark 2011) in human fMRI. Interestingly there was a notable dissociation of navigation-related fMRI activations in the medial temporal lobe: in contrast to the hippocampal activation, which was specific to movement initiation, the reverse fMRI contrast (stationary versus movement initiation) showed bilateral activation of the posterior parahippocampal cortex, consistent with its role in static scene processing (Epstein 2008).

Increased bilateral hippocampal fMRI activity related to movement initiation was seen in participants who showed better subsequent memory for the object locations. This finding suggests a link between the process of self-directed movement initiation and encoding efficiency within this task, consistent with previous findings relating hippocampal activation during encoding with subsequent memory performance (Schacter et al. 1998; Davachi et al. 2003 for review see Paller & Wagner 2002).

The presence of a performance-related increase in theta power during active exploration provides a possible link to human behavioural and fMRI studies of active versus passive learning enhancements derived from the hippocampal-dependent volitional control network (Voss et al. 2011). Voss and colleagues (2011) demonstrated that the hippocampus supports volitional control of exploratory behaviour so as to optimize learning of object locations. There is significant overlap between this concept and the hypothesized functional role for hippocampal theta in behavioural control of exploration, active movement during a spatial memory task being an example of the active control of learning (O'Keefe & Nadel 1978; Morris 2006; O'Keefe 2006). Thus in accordance with O'Keefe and Nadel, I propose that movement-related theta may aid in signalling the potential for volitional control of encoding, which is consistent with findings in rodents showing increased hippocampal theta power for volitional versus deterministic movement (Song et al. 2005; Terrazas et al. 2005) and humans showing increased hippocampal theta power for goal-directed versus aimless movements (Cornwell et al. 2008). Notably, the possibility that movement-related theta interacts with performance-related influences on theta is further supported by my finding that both theta power and hippocampal activity for movement initiation relative to stillness correlate with performance during navigation, a time period where the participant has active control over how he or she encodes a particular spatial representation.

Although I measured theta power and hippocampal blood oxygen level-dependent (BOLD) signal increases in the same 1-s time periods corresponding to navigation behaviour and memory performance in the same participants, I do not assume a direct correlation between BOLD and theta oscillatory power. The relationship between BOLD and hippocampal theta is unclear. Past work by Ekstrom

and colleagues has shown decoupling between hippocampal BOLD and theta, despite findings that BOLD and theta may negatively correlate elsewhere in the brain (Ekstrom et al. 2009; Meltzer et al. 2009). It should be noted that rodent hippocampal theta has been found to positively correlate with brain tissue oxygenation (McHugh et al. 2011). Additionally, it is important to emphasize that even the MEG signals on temporal sensors were not being measured specifically from the hippocampus, although I note that the analogous aspects of theta oscillations in rodents (Grastyan et al. 1959; Vanderwolf 1969; O'Keefe & Nadel 1978; Jeewajee et al. 2008) are known to depend on the septo-hippocampal system. Unlike the performance effect during the 3-s Cue Period, I was not able to localize the source of the movement-initiation related theta increase, possibly because its transient nature did not allow good frequency resolution. In my experiment, the participants typically moved in 1-s periods, precluding the investigation of longer time windows. Longer periods of continuous virtual movement would allow us to better investigate induced low frequency activity in the hippocampus, as seen in other experiments (Ekstrom et al. 2005; Watrous et al. 2011).

Given the literature in rodents (Hyman et al. 2005; Jones & Wilson 2005a) and humans (Klimesch 1996; Brown et al. 2010; Jacobs & Kahana 2010) showing hippocampal-prefrontal interactions during spatial navigation, I investigated the MEG signal from both regions. Consistent with this literature, I found virtual movement-related theta in both the frontal midline and hippocampus (Fig. 14). Numerous studies have also found task-related midline frontal theta power and phase changes during successful memory encoding and maintenance (for reviews see Klimesch, 1996; Mitchell et al., 2008; Jacobs and Kahana, 2010). These performance effects are thought to underpin key neocortical-hippocampal interactions in learning

and memory. Future research will investigate the probable frontal midline and hippocampal sources of the theta-band signals reported here, and their potential interactions with other brain regions (Lisman et al. 2008; Colgin et al. 2009; Penny et al. 2009; Fell & Axmacher 2011).

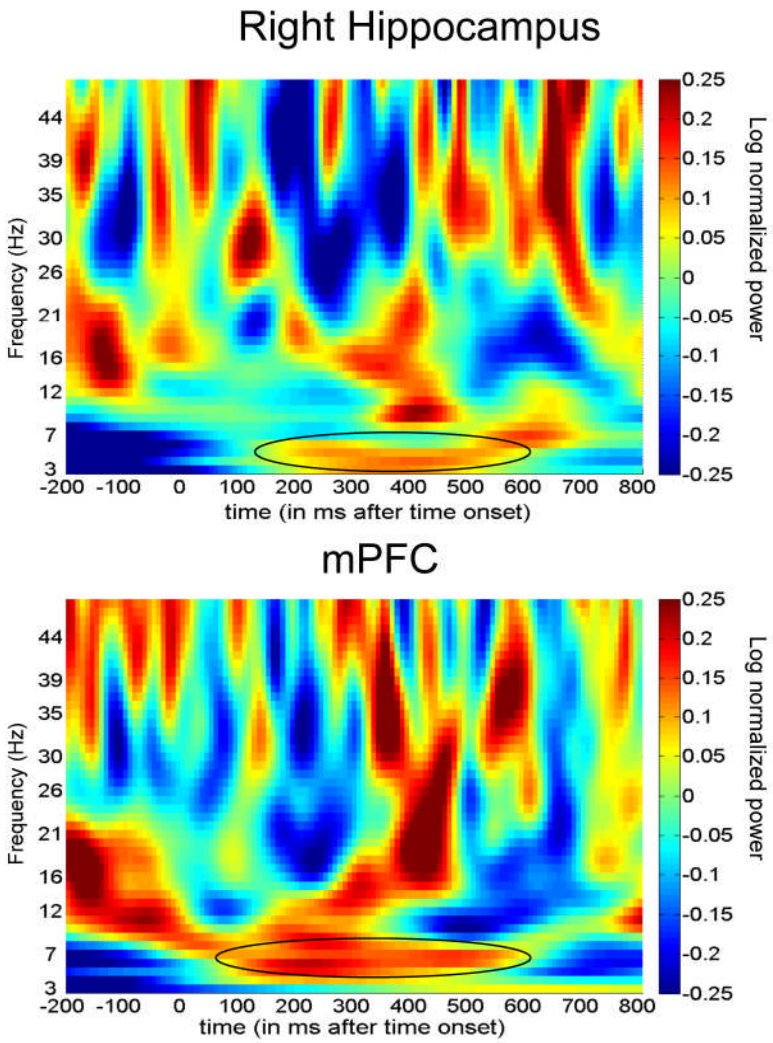

Figure 14: mPFC and hippocampus source extraction

Beamformer leadfield source extraction from Right Hippocampus (fMRI coordinates from Figure 4A; x = 24; y = −6; z = −18) and medial PFC (x = 10; y = 30; z = 22) to compare midline prefrontal and hippocampal theta during the Movement Initiation effect shown on the sensor level in Figure 9A–B.

My performance correlates of theta power complement previous MEG work looking at medial temporal lobe theta power before the onset of an encoding trial (Guderian et al. 2009; Addante et al. 2011; Fell et al. 2011) and increased theta power for successfully encoded memories during mnemonic processing (Klimesch et al. 1996; Tesche & Karhu 2000; Sederberg et al. 2003; Osipova et al. 2006; Rutishauser et al. 2010). Furthermore, by showing enhanced subsequent memory effects during virtual movement over stationary periods, this is the first study to my knowledge that implicates self-initiated movement-related theta increases with self-directed learning.

The hippocampus and corresponding theta oscillations have been hypothesized as a network hub (Buckner et al., 2008; Battaglia et al., 2011) and global signal integrator (O'Keefe, 2006) for information from around the brain. The potential role for hippocampal theta for guiding self-directed learning paves the way to investigate how theta and hippocampal-related active control mechanisms interact with a wide range of networks responsible for dynamic evaluative behaviours like planning and novelty processing (Axmacher et al. 2010; Benchenane et al. 2010; Rutishauser et al. 2010) in which theta power and synchrony changes have been observed. For instance, evaluative behaviours relating to emotion and anxiety have been associated to theta (Gray 1982). Theta synchronization in rodents has been observed between the hippocampus and the amygdala during fear learning (Seidenbecher et al. 2003) and between the hippocampus and medial prefrontal cortex during anxiety (Adhikari et al. 2010). Hippocampal theta dysfunction related to learning control dynamics during encoding could possibly represent core pathology in mental illnesses, where feelings of helplessness (i.e., lack of control) in

certain environments are common, such as post-traumatic stress disorder (PTSD) and depression (Gould et al. 2007; Cornwell et al. 2010).

4.5 Conclusions

In summary, my results indicate the key role movement and the resulting self-initiated dynamic control of spatial encoding have in generating human theta oscillations and supporting hippocampal mnemonic function. Further studies into oscillatory characteristics and functional networks associated with the hippocampus and volitional learning will be necessary to clarify the role hippocampal theta has in the control of active learning. By using an interactive ecologically realistic experimental task and multi-modal neuroimaging to investigate hippocampal function, my results show that an analogue of Type I theta in the rodent hippocampus can be found in humans. Although I did not manipulate self-directed versus non-self-directed learning directly, my results still suggest that the human hippocampal theta rhythm could serve to coordinate self-directed learning.

Chapter 5

*Experiment 2: Medial prefrontal theta phase coordination of spatial memory retrieval**

*This chapter derives partly from Kaplan R[#], Bush D[#], Bonnefond M, Bandettini PA, Barnes GR, Doeller CF, Burgess N (under review) Medial prefrontal theta phase coordination of spatial memory retrieval.

# denotes equal contributors

Precis

In experiment 1, I found that a potential analogue of the type I theta rhythm measured in rodents could be measured non-invasively in humans during virtual movement initiation. In addition, virtual movement initiation in a parallel fMRI task caused increased BOLD activity in the hippocampus. Both fMRI and theta power changes also correlated with memory performance. During a cued retrieval phase, there was a significant increase in hippocampal theta for trials with objects that were subsequently more accurately retrieved versus trials with objects that were subsequently less accurately retrieved. This finding motivated me to investigate changes in power and interregional phase coherence during this cue period versus baseline. I hoped to find increases in medial prefrontal theta and neocortical gamma power during the cue period, and was interested to determine whether phase interactions between these oscillatory sources might occur during this period.

5.1 Introduction

Memory retrieval is thought to depend on coordination of multiple brain regions and recent theories posit that communication between the hippocampus and neocortex, particularly the medial prefrontal cortex (mPFC), play a critical role in long-term memory formation (e.g., Frankland & Bontempi 2005; Wang et al. 2010; Battaglia et al. 2011; Hyman et al. 2011). One hypothesized mechanism for communication between these regions is oscillatory coupling. In rodents, theta oscillations are prominent in the hippocampal formation during spatial exploration (Grastyan et al. 1959; Vanderwolf 1969, O'Keefe & Nadel 1978) and theta is also associated with mnemonic function (Winson 1978). In humans, both the medial temporal lobe (MTL) (Cornwell et al. 2008; Guderian et al. 2009; Rutishauser et al.

2010; see Duzel et al. 2010 for review) and frontal midline (Klimesch et al. 2001; Summerfield & Mangels 2005; Griesmayr et al. 2010; Addante et al. 2011; see Mitchell et al., 2008 for review) theta rhythms have been correlated with mnemonic function. Rodent studies also implicate theta coupling between hippocampus and mPFC in goal-directed exploration (Hyman et al., 2005; Jones & Wilson, 2005a; Siapas et al., 2005). Furthermore, recordings from the surface of prefrontal and parahippocampal cortices in humans suggest that coordinated low-frequency phase-locking between the MTL and regions including the PFC are related to successful memory retrieval (Watrous et al. 2013).

In a parallel line of research, experimental and theoretical studies have described hippocampal theta phase modulation of both local and neocortical gamma amplitude, and implicate this mechanism in memory maintenance (Jensen & Lisman 1996; Fries 2005; Lisman & Buzsaki 2008; Schroeder & Lakatos 2009; Canolty & Knight 2010; Jutras & Buffalo 2010; Fell & Axmacher 2011; Maris et al. 2011). These ideas have gained traction with data from rodent and human electrophysiology that demonstrates theta phase modulation of gamma amplitude during mnemonic function (Bragin et al. 1995; Mormann et al. 2005; Canolty et al. 2006; Colgin et al. 2009; Tort et al. 2009). Increases in gamma power across occipital regions during visual perception are well documented (Gray & Singer 1989; Tallon-Baudry & Bertrand 1999; Hall et al. 2005; Hoogenboom et al. 2006; see Fries 2005 for review), and these studies raise the possibility that frontal midline theta may also modulate gamma amplitude in multiple task-relevant cortical regions (Sirota et al. 2008; see Jutras & Buffalo 2010 for review).

I used MEG to measure theta and gamma power across the whole brain during cued retrieval of objects' locations within virtual environments and examined

inter-regional phase locking and cross-frequency coupling during this time period, compared to a baseline period of quiet fixation.

5.2 Methods

5.2.1 *Participants*

Seventeen right-handed male participants gave written consent and were compensated for performing the experimental task, as approved by the local research ethics committee. All participants had normal or corrected-to-normal vision and reported to be in good health with no prior history of neurological disease. Further information about participants, stimuli, task, data acquisition and preprocessing can be found in Experiment 1, in which the same data were analysed for changes in spectral power related to performance.

5.2.2 *Procedure*

Participants navigated freely in a virtual environment projected onto a screen in front of them, using a button box with their right hand to move the virtual viewpoint. In each session, they had to collect and encode the location of six different objects in the environment, three times each (three objects in each of two practice sessions). Object location was constant within each session. Having completed this exploration phase, participants' memory for the object locations was then tested in retrieval trials. In each retrieval trial, a 4s inter trial interval (ITI) composed of blink phase and baseline fixation period was followed by a 3s cue period during which an image of one object was presented on screen, and participants were subsequently asked to navigate to the remembered location of that

object and make a response (Fig 15a). There were six sessions (with two practice sessions before scanning), where participants would learn and remember the location of six different objects per session (for more task details see Experiment 1). To examine performance related effects, the distance error between real and remembered object locations was calculated for each trial and trials then split according to whether that value was greater or lower than that participant's median distance error.

5.2.3 *MEG Source Reconstruction*

The linearly constrained minimum variance (LCMV) scalar beamformer spatial filter algorithm from SPM8 was used to generate source activity maps in a 10 mm grid (Barnes et al. 2003). Co-registration to MNI coordinates was based on three fiducial points: nasion and left and right preauricular. The forward model was derived from a single-shell model (Nolte & Curio 2000) fit to the inner skull surface of the inverse normalized SPM template. The beamformer source reconstruction consists of two stages: firstly, based on the data covariance and lead field structure, weights are calculated which linearly map sensor data to each source location; and secondly, a summary statistic based on the change in oscillatory power between experimental conditions is calculated for each voxel. In this case, the summary statistic computed is the change in 4-8 Hz, 30-45Hz or 65-85Hz power normalized by the projected sensor white noise power, and the time periods under comparison are 0.5-1.5s after cue onset (corresponding to the period of performance-related hippocampal theta power differences observed in Experiment 1) and a 1s baseline period prior to cue onset (Fig 15a). My choice of low (30-45 Hz) and high (65-85 Hz) gamma frequency bands was based on previous studies in the rodent medial

temporal lobe investigating the interaction between theta and low/high gamma (Bragin et al. 1995; Colgin et al. 2009)

In order to ascertain whether any of the theta phase coupling effects could be an artefact of increases in oscillatory power or eye movements during the cue period, oscillatory power and eye movement variance values (the latter identified through independent component analysis of the raw MEG signal from all sensors using EEGlab; Delorme et al. 2004 and the FieldTrip software package; Oostenveld et al. 2011) were computed for all voxels in all trials. Variance in the theta phase coupling measure for all trials that could be explained by oscillatory power (in both seed and target voxels; Muthukumaraswamy & Singh 2011) and eye movement variance was subsequently removed by linear regression, and statistical analysis of differences in theta phase coupling between baseline and cue periods was then performed on the residual values.

5.2.4 *Phase Locking*

Instantaneous phase was obtained by applying the Hilbert transform to the 4-8Hz band-pass filtered time-series obtained in source space using the LCMV beamformer algorithm. Two metrics were then used to quantify theta phase coupling between a single seed voxel and every other voxel in the brain. The seed voxel for each participant was chosen as that with the greatest theta power increase between baseline and cue periods within 20mm of the group maximum co-ordinates, in order to account for the observed variance in frontal midline theta source location between participants (Ishihara et al. 1981; Mitchell et al. 2008). Firstly, I examined changes in circular variance of the phase difference between the seed voxel and the voxel in

question across each 1s baseline and cue epoch. A significant decrease in the circular variance indicates that the phase difference between filtered oscillatory signals in the two voxels has become less variable over time. Secondly, I also used the phase lag index (PLI) to assay theta coupling between voxels, which is designed to avoid volume conduction by ignoring any coupling at zero phase-lag (Stam et al. 2007). Briefly, this entails assigning a value of +1 or -1 to each time step depending on whether the phase difference between seed and source voxels is positive or negative. For each trial, the PLI then corresponds to the absolute value of the mean of these values (which will tend to zero for randomly distributed phase differences and to one for a consistent non-zero phase relationships). The circular variance or PLI values for each trial are then averaged for each condition before being entered into a second level statistical analysis.

5.2.5 *Phase-Amplitude Coupling*

To investigate possible theta phase modulation of gamma amplitude, we again examined circular variance of the difference between a single theta phase seed and the phase of gamma amplitude in all other voxels across the brain within each trial (Lachaux et al. 1999; Penny et al. 2008). Briefly, instantaneous high gamma (65-85 Hz) amplitude in each voxel was obtained by applying the Hilbert transform to the band-pass filtered time series obtained using the LCMV beamformer algorithm. This gamma envelope was then band-pass filtered in the 4-8 Hz theta range, the instantaneous phase of that envelope obtained by applying the Hilbert transform for a second time, and circular variance of this phase difference calculated for all voxels in the brain.

5.2.6 *Statistical Analysis*

For each of the analyses described above, the summary images for each participant were entered into a second level one-sample t-test in SPM8 with a significance threshold of $p<0.001$ uncorrected (cluster extent of at least 5 voxels) for multiple comparisons across the whole brain volume, unless specified otherwise. All images are displayed on the SPM8 canonical average MNI 152 T1 image at a significance level of $p<0.001$ uncorrected, for display purposes, unless specified otherwise

5.3 Results

5.3.1 *Theta Power Changes and Source Reconstruction*

I utilized the linearly constrained minimum variance (LCMV) beamformer algorithm (Barnes et al. 2003) in SPM8 (Litvak et al. 2011) to estimate cortical sources that exhibited significant increases in theta (4-8Hz), low (30-45Hz) and high (65-85Hz) gamma power between the baseline and cue periods. We identified a single mPFC peak activation in the theta band that cleared our significance threshold of $p<0.001$ uncorrected (x=0; y=58; z=22; Z-score=4.39; Fig. 15b). In the low gamma band, no significant sources were identified. In the high gamma band, we identified a significant activation with three distinct peaks in the visual cortex (x=10, y=-92; z=24; Z-score=4.00; second peak: x=-8; y=-86; z=36; Z-score=3.79; Fig. 15c) and precuneus (x=-4; y=-50; z=34; Z-score=3.80), presumably due to the visual response induced by the presentation of the cue (Gray & Singer 1989; Tallon-Baudry & Bertrand 1999; Hall et al. 2005; Hoogenboom et al. 2006). A regression of trials was performed on trial by trial values of eye movement variance, ruling out any confounding effects of eye movements see Methods.

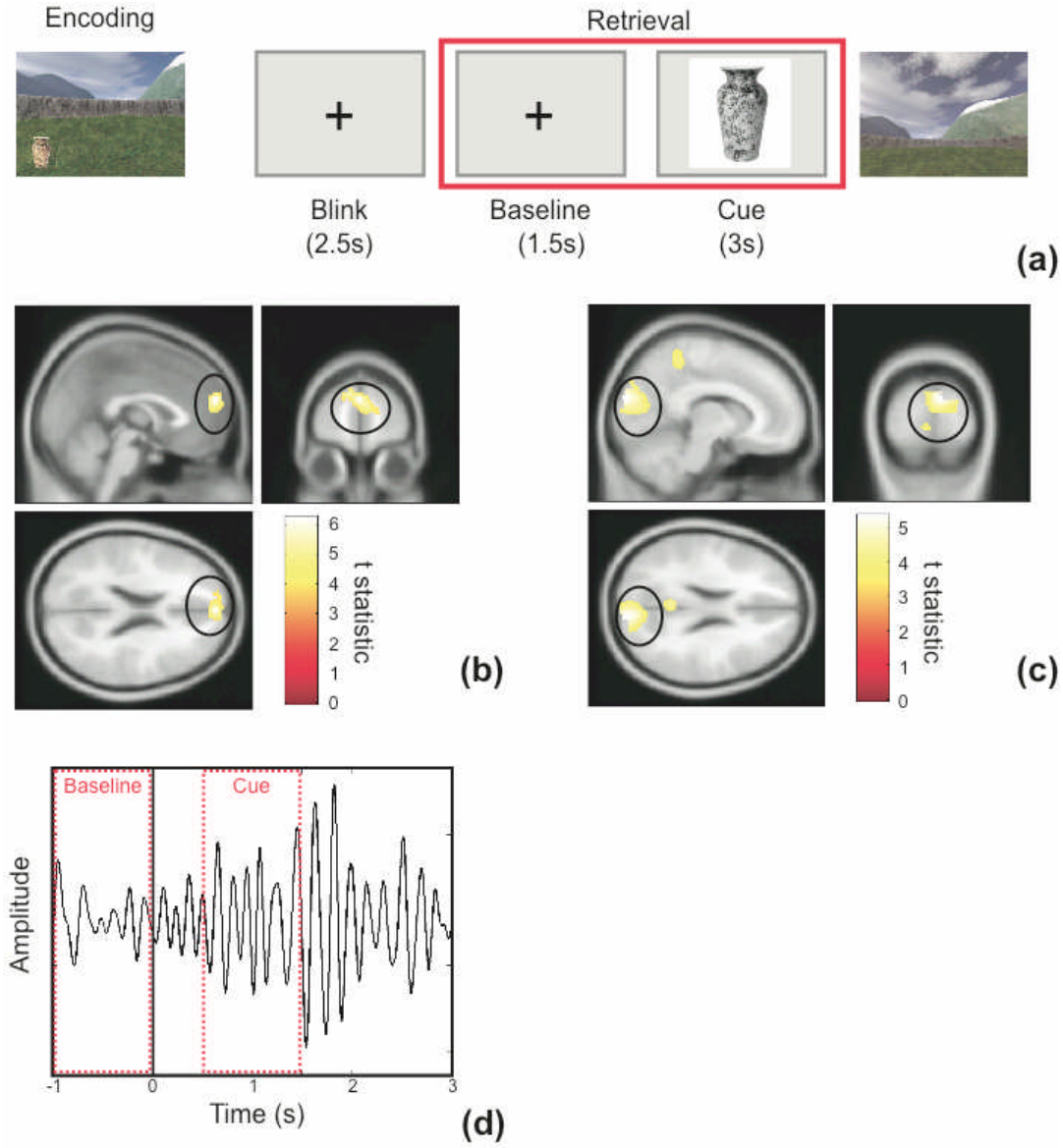

Figure 15: Task structure and oscillatory power changes

(a) Structure of the experiment. Participants first navigate freely in a virtual environment and encode object locations during a learning period. After a short break their memory for these object locations is tested. During these trials a 1s baseline fixation period is followed by a 3s cue period (highlighted by the red box), where an image of one object is presented on screen. Participants are subsequently required to navigate to the object's location in the environment and make a response. **(b)** 4-8 Hz theta power source reconstruction showing a significant increase in the mPFC (peak: x=0; y=58; z=22; Z-score: 4.39) between the baseline and cue periods. **(c)** 65-85 Hz high gamma power source reconstruction showing a significant increase in the visual cortex (peak: x=10; y=-92; z=24; Z-score: 4.00) and precuneus (peak: x=-4; y=-50; z=34; Z-score: 3.80) during the cue period compared to baseline.

(d) Sample trace for the baseline and cue periods extracted from the peak mPFC theta voxel and filtered in the 4-8Hz band.

5.3.2 *Theta Phase Coupling*

Next, I used the frontal midline region that exhibited a significant theta power increase between baseline and cue periods as a seed region to investigate changes in theta phase coupling across the whole brain. The specific seed voxel for each participant was chosen as that with the greatest theta power increase between baseline and cue periods within 20mm of the group maximum, in order to account for the variance in frontal midline theta source locations between participants (Ishihara et al. 1981).

To assay changes in theta phase coupling during cue versus baseline periods, we looked for decreases in circular variance in the difference between the theta phase of our mPFC seed region and the theta phase in other voxels in the brain. I found increased theta phase coupling (i.e., decreased circular variance) in the right anterior medial temporal lobe (aMTL) between baseline and cue periods (x=20; y=-16; z=-26; Z-score=4.52; Baseline circular variance = 0.64±0.0072; Cue circular variance = 0.62±0.0061; Fig. 16a, c).

Next, I made use of the phase lag index (PLI) metric (Stam et al., 2007) to rule out that our mPFC-aMTL circular variance theta coupling effect was due to volume conduction. In accordance with our circular variance effect, I also identified a significant increase in PLI between the mPFC seed region and the right anterior medial temporal lobe between baseline and cue periods (x=22; y=-24; z=-22; Z-score=3.48; Baseline PLI = 0.29±0.0086; Cue PLI = 0.32±0.0092; Fig. 16b). I also observed significant increases in the PLI with other nearby anterior cingulate cortex (ACC) and midline - but not lateral - PFC regions.

Regression analyses indicate that these increases in theta phase locking are not significantly correlated with changes in eye movement variance (Muthukumaraswamy & Singh 2011) or oscillatory power in seed and source voxels between conditions, see Methods.

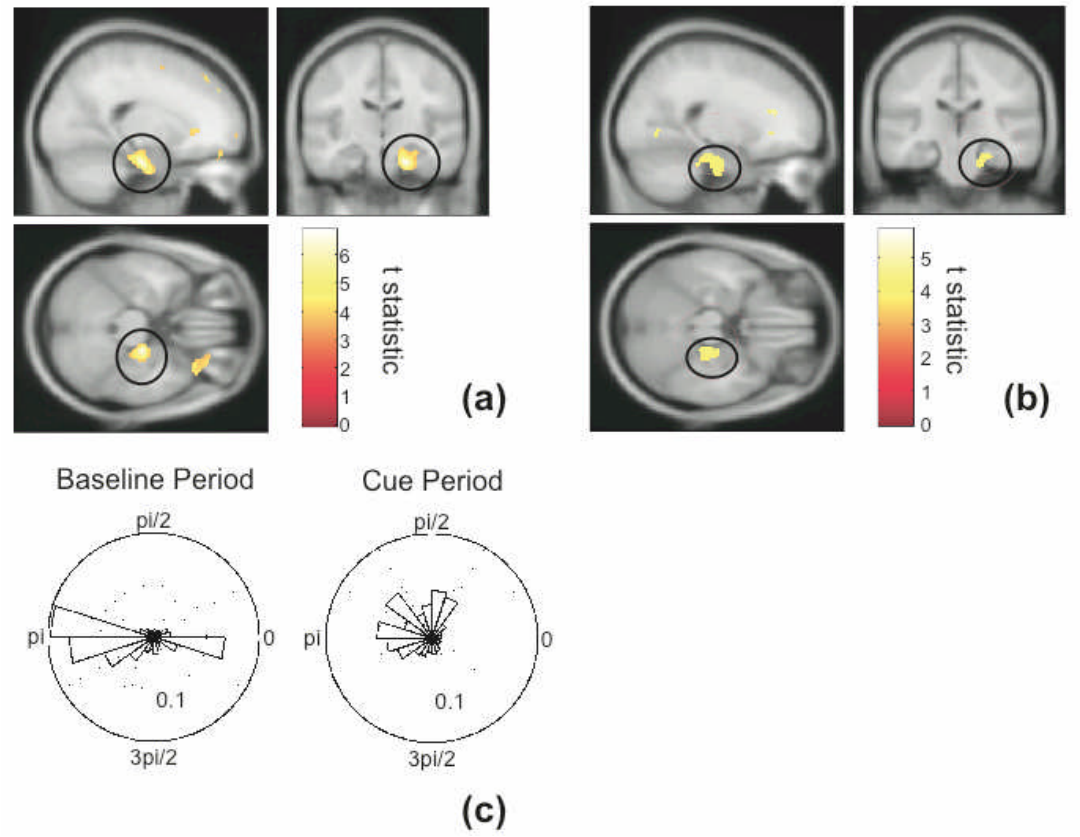

Figure 16: mPFC-aMTL theta coupling during retrieval

Images of right aMTL showing a significant increase in theta phase coupling with the mPFC seed location between the baseline and cue periods, shown using **(a**) decrease in circular variance of theta phase differences (peak: x=20; y=-16; z=-26; Z-score=4.52) and (**b**) phase lag index (PLI, peak: x=22; y=-24; z=-22; Z-score=3.48). **(c)** Circular histogram of theta phase differences between the mPFC seed and aMTL voxel corresponding to the group peak at each time point during a typical baseline and cue period (with circular variance values close to the group mean; baseline period = 0.71, cue period = 0.64). Note the narrower distribution of phase differences during the cue period.

5.3.3 *Theta Phase – Gamma Amplitude Coupling*

Having identified an increase in mPFC-aMTL theta phase coupling between baseline and cue periods, I then used the frontal midline theta source as a seed region to explore theta phase modulation of gamma amplitude across the whole brain. I examined increases in phase coupling (i.e. decrease in the circular variance of phase differences) between mPFC theta and gamma amplitude between baseline and cue periods in all other source space voxels. I found the most significant increase in coupling between baseline and cue periods in medial parietal cortex extending into the posterior parahippocampal cortex(x=32; y=-66; z=16; Z-score=4.77; Fig. 17). Additionally, I found significant increases in theta phase-gamma amplitude coupling between the mPFC seed and small clusters in right lateral PFC and left visual cortex (see Table 5). Regression analyses indicate that these increases in theta phase locking are not significantly correlated with changes in eye movement variance (Muthukumaraswamy & Singh 2011) or oscillatory power in seed and source voxels between conditions. However, power-power mPFC-MTL theta-theta and mPFC-visual cortex theta-gamma coupling did predict subsequent memory performance, which will be a topic of further investigation.

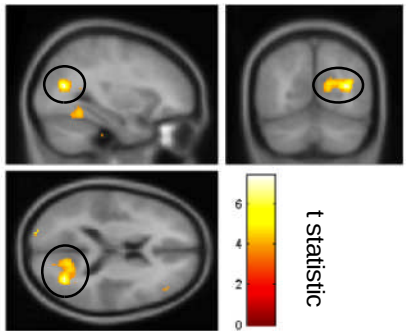

Figure 17: **mPFC theta phase coupling with medial parietal gamma amplitude** mPFC theta phase coupling with high gamma amplitude in medial parietal cortex during cued spatial memory retrieval. Images showing a decrease in the circular

variance of phase differences in the medial parietal cortex (peak: x=32; y=-66; z=-16; Z-score=4.77) between mPFC seed theta phase and the phase of gamma amplitude between the baseline and cue periods.

Region	***x***	***y***	***z***	**Z-score**
R Medial Parietal Cortex/Parahippocampal Cortex	32	-66	16	4.77
R Lateral Prefrontal Cortex	46	38	10	3.85
L Visual Cortex	-14	-92	2	3.49

Table 3. mPFC theta phase coupling with gamma amplitude

5.4 Discussion

I have identified an increase in mPFC theta power during the cued retrieval of learned spatial representations compared to a preceding baseline period of quiet fixation (Fig. 15b) and demonstrated increased coupling between the phase of this mPFC theta signal and both the phase of ongoing theta oscillations in the right aMTL (Fig. 16) and the amplitude of gamma oscillations in medial parietal cortex extending into the posterior parahippocampal cortex(Fig. 17), left visual cortex and right lateral PFC during this period(Table 5).

The observed increase in mPFC theta power suggests that the mPFC plays a role in initiating memory retrieval. Frontal midline theta power increases around the time of memory recall are frequently observed in EEG studies (Klimesch et al. 2001; Summerfield & Mangels 2005; Griesmayr et al. 2010; Addante et al. 2011), including spatial memory tasks in rodents and humans (Kahana et al. 1999; Young & McNaughton 2009). Human MEG studies have identified frontal midline theta sources localized in both anterior cingulate cortex and mPFC regions (Asada et al. 1999; Ishii et al. 1999) and further research is needed to determine whether theta in the anterior cingulate cortex (ACC) and mPFC can be dissociated by behavioral relevance (e.g. supporting cognitive control vs. memory retrieval).

Increased theta phase coupling between mPFC and right anterior MTL during cued spatial memory retrieval supports a role for interregional theta coupling in memory. Interactions between these two regions are thought to support memory consolidation (for review see Frankland & Bontempi 2005) and rodent studies have demonstrated increased mPFC-MTL theta phase coupling during spatial memory tasks (Hyman et al. 2005; Jones & Wilson 2005; Siapas et al. 2005). It is interesting to note that the presence of increased MTL-mPFC theta phase coupling at decision points during rodent spatial working memory tasks (Jones & Wilson 2005; Benchenane et al. 2010; see Euston et al. 2012 for review) mirrors recent observations of increased theta coupling between these regions during human decision-making tasks (Guitart-Masip et al. 2013). In my data, the location of the aMTL theta signal most strongly coupled with mPFC (Fig. 16) is in the vicinity of entorhinal cortex (EC), consistent with models describing the role of this region in mnemonic function (Miller 1989; Bragin et al. 1995; Hasselmo et al. 2002; Colgin et al. 2009). Recent invasive direct (Suthana et al. 2012) and indirect (Hamani et al. 2008; Laxton et al. 2010) stimulation studies in humans have highlighted the importance of EC as a pathway for the hippocampal theta rhythm's neocortical interactions, see also (Mormann et al. 2008) for evidence of separate theta rhythms in the EC and hippocampus.

My observation of increased gamma power in the visual cortex during cue presentation follows a large body of experimental work (Gray & Singer 1989; Tallon-Baudry & Bertrand 1999; Hall et al. 2005; Hoogenboom et al. 2006; for review see Fries 2005). I also observed increased gamma power in the precuneus, an area implicated in memory retrieval (Wagner et al. 2007) and imagery (Fletcher et al. 1996; Byrne et al. 2007), which is consistent with previous findings relating high

frequency gamma oscillations in the parietal midline to performance during mnemonic tasks (Morgan et al. 2011; Foster et al. 2012). Local computations in the cortex are thought to be facilitated by gamma oscillations (see Fell et al. 2001; and reviews by Hermann et al. 2004; Jensen et al. 2007 for examples in memory) and are potentially modulated by the phase of lower frequency oscillations such as theta (Fries 2005; Canolty et al. 2006; Lisman & Buzsaki 2008; Schroeder et al. 2009, Sauseng et al. 2010; Jutras & Buffalo 2010; Fell & Axmacher 2011; Maris et al. 2011). Recent MEG and intracranial EEG studies have implicated local MTL theta-gamma coupling in the maintenance of working memory (Axmacher et al. 2010; Fuentemilla et al. 2010; Poch et al. 2011). My findings suggest that human mPFC theta temporally coordinates medial parietal gamma, with aMTL theta, during spatial memory retrieval (Bragin et al. 1995; Sirota et al. 2008; Colgin et al. 2009; Tort et al. 2009) although further work is necessary to characterise whether these changes are due to task versus rest changes or specific to cued memory retrieval. Furthermore, artefactual power coupling between mPFC theta and both visual gamma and MTL theta warrants further investigation of how these artefactual changes in coupling correlated with relevant behaviour.

5.5 Conclusions

In sum, my findings suggest that theta oscillations in mPFC work in tandem with aMTL theta to coordinate incoming perceptual representations from medial parietal cortex during cued spatial memory retrieval. This suggests that human frontal midline theta generated in the service of memory retrieval has a tangible link with theta rhythm generated by the medial temporal lobe, and supports the hypothesis that coupling of theta rhythms with neocortical gamma oscillations serves

to rapidly recruit information from distant neocortical sites (Sirota et al. 2008; Buzsaki & Wang 2012).

Chapter 6

*Experiment 3: The neural correlates of environmental and object novelty during exploratory learning.**

*This chapter derives partly from Kaplan R, Horner AJ, Bandettini PA, Doeller CF, Burgess N (submitted) Separating the content from the context: novelty processing in the temporal lobe.

Precis

In experiment 1, I found that environmental, but not object novelty modulated a correlate of the type I theta rhythm during virtual navigation. As a result, I was interested in the anatomical distinction between environmental versus object novelty in the same task, so I used fMRI with this complete task including novelty manipulations from experiment 1. I hoped to determine where in the temporal lobe object and environmental novelty processing occurs during spatial learning. Thus, potentially resolving the debate over whether the hippocampus is a generalized novelty detector. Given past surprising findings implicating the amygdala in novelty detection, I was interested in determining whether it might be involved in initial learning of novel objects in this task given past results from human and rodent invasive recordings.

6.1 Introduction

When exploring our environment, we constantly come across new information and our encounters with novelty are multi-faceted. We must react to changes in our overall surroundings, but also simultaneously detect the novel content located within our environment. How the brain processes these different forms of novelty during learning is unknown. A prime candidate for a role in novelty detection is the hippocampus (Stern et al. 1996; Knight 1996; Strange et al. 2005; Kumaran et al. 2006; for reviews see Martin 1999; Ranganath & Rainer 2003; Nyberg et al. 2005), an area normally associated with human mnemonic function. However, there are differing accounts from human and rodent models of the hippocampal system about whether the hippocampus serves as a generalized novelty detector (Sokolov 1963), or responds primarily to novel contexts (Kumaran et al.

2006; Good et al. 2007). Human intracranial EEG (iEEG) and fMRI data and studies in animal models have also implicated medial temporal lobe (MTL) areas such as the perirhinal cortex (Buckley et al. 1998; Pihlajamaki et al. 2003; for review see Brown and Aggleton 2001), pre-rhinal/parahippocampal cortex (Bussey et al. 1999; Epstein et al. 1999; Preston et al. 2010), and the amygdala in novelty detection (Halgren et al. 1980; Fried et al. 1997; Rutishauser et al. 2010; Moses et al. 2002; Sheth et al. 2008; Farovik et al. 2011).

I attempted to dissociate environmental and object novelty with an object-location fMRI study that makes both environmental and object novelty behaviourally relevant within a spatial memory paradigm, similar to tasks used with rodents. In my virtual navigation task, participants used a button box to learn and navigate to the location of novel or previously learned objects in a session, where the objects were located in either a novel or previously explored virtual environment (see Fig 19). After completing the learning/encoding phase of a session, participants had a test/retrieval phase for each object's location. Immediately after being cued by a picture of a previously learned object, participants were placed in the virtual environment and had to navigate to the location where they had encountered the object and press a button (i.e., “replace” it) to conclude the trial (see Fig. 18B-C). Given previous evidence from the animal literature, I hypothesized that separate novelty responses in the MTL during the encoding of object locations would be observed (Moses et al. 2002), relating to object novelty and environmental novelty, and potentially over different time scales.

6.2 Methods

6.2.1 Participants

Twenty right-handed male participants (mean age yrs=23.89; SD=3.71 years; range=18-33) gave written consent and were compensated for performing the experimental task, as approved by the local Research Ethics Committee at University College London. All participants were right-handed with normal or corrected-to-normal vision and reported to be in good health with no prior history of neurological disease. Two participants were excluded because of scanner malfunction. Eighteen right-handed male participants were therefore analyzed for the fMRI dataset.

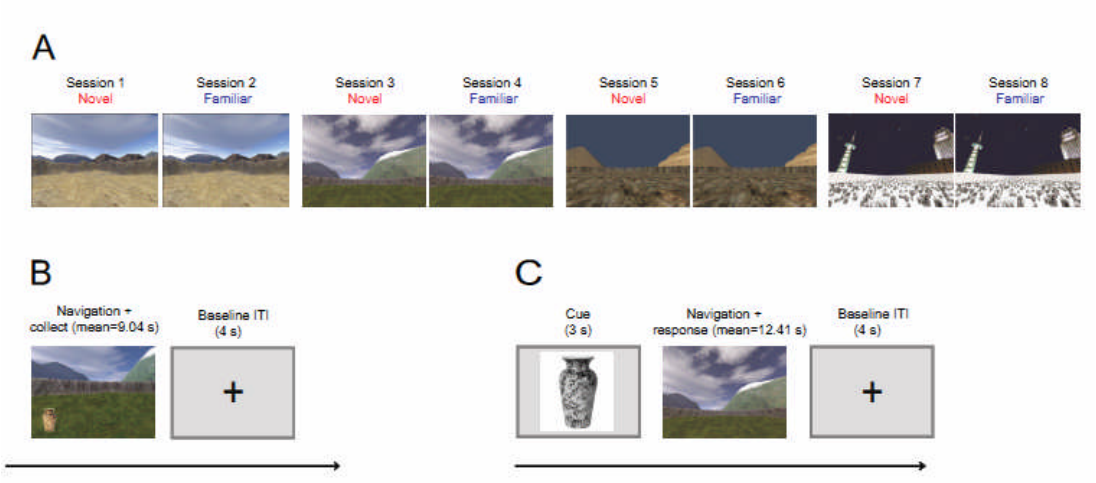

Figure 18: Experimental design

(A) Experimental environments shown from the participants' (first-person) perspective. Four different environments are presented in eight experimental sessions. The first two sessions (always the desert environments) provided practice outside of the scanner. Sessions 3-8 contained three novel-familiar environment repetitions with environment order, counterbalanced across participants. (B) Encoding/Learning phase trial structure. During encoding trials, participants use a button box to navigate and "collect" 3 novel and 3 familiar (previously presented) objects (vase shown as example) 4 times each (a total of 24 trials per session). (C) The test phase, trial structure. After being cued for 3 s with a picture of an object that had been collected in the encoding phase of the current session, participants were placed back in the environment and had to navigate to where they thought the object had been located during that learning period.

6.2.2 Stimuli, Task, and Trial Structure

As in Experiments 1 and 2, the experiment was composed of eight sessions. The first two sessions were practice sessions in the same virtual desert environment, conducted on a laptop outside the MRI scanner. The participants familiarized themselves with the environment by navigating around and then collecting objects in the environment by running into them and then being tested on their previous location. These practice sessions lasted for about 2-3 min.

During the fMRI sessions, an individual trial consisted of a participant being randomly placed in an environment and having to navigate towards an object to collect it and to remember its location (average duration 9.04 s per trial). Participants had four trials to learn the location for each of the six objects interleaved in a set of 24 trials. Next participants were presented with a grey screen with a crosshair for 4-s between trials. After the learning phase was completed there was a 30-s inter-phase rest period, when instructions on the next phase (test phase) were presented. The test phase for the location of each of the six collected objects started with a 3-s period in which an object was presented on a gray background (cue phase). Participants were then placed at a random location in the environment and told to navigate to the spot where they believed the pictured object had been located (average duration= 12.41 s). They then pressed a button to or indicate its previous location. Once the button was pressed the ITI period would begin again for 4-s.

6.2.3 Procedure and Design

Participants were instructed that they were going to navigate through a virtual environment over multiple sessions using a button box, and that they would have to pick up several different objects (six) in the environment, four times each (three

objects, three times each for the two practice session). The order of trials was randomized (but unknown to participants) separated into three mini-blocks. Object location never changed within a session. After they completed this exploration phase, they were tested at the end in a test period, described above.

During the fMRI portion of the experiment, a new environment was presented and then re-presented at the next session as a familiar environment. This occurred on four occasions (three in the fMRI component), so that half of the eight environments were novel (refer to Figure 18A). Each environment arena had the same area, but had its own unique shape (square, circle, triangle, and rectangle) and textures (desert, grass, snow, rocky textures; refer to figure 18) differentiate the environments.

Participants were presented with counterbalanced familiar or novel objects within each environment. Following the practice sessions, the objects presented in an environment were comprised of object that the participants had either collected ("familiar") or not collected ("novel") in a previous session. Familiar objects were always from different environments in the fMRI experiment and the first familiar objects were introduced during the practice session outside of the scanner.

6.2.4 fMRI Acquisition

Functional images were acquired on a 3T Siemens Trio scanner. Blood oxygenation level dependent (BOLD) T2*-weighted functional images were acquired using a gradient-echo EPI pulse sequence acquired obliquely at =45 degrees with the following parameters: repetition time, 3,360 ms; echo time, 30 ms; slice thickness, 2 mm; interslice gap, 1 mm; in-plane resolution, 3x3 mm; field of view, 64x72 mm^2; 48 slices per volume. A field-map using a double echo FLASH

sequence was recorded for distortion correction of the acquired EPI (Weiskopf et al. 2006). After the functional scans, a T1-weighted 3-D MDEFT structural image (1 mm^3) was acquired to co-register and display the functional data.

6.2.5 fMRI Data Analysis

Statistical analyses were performed using a univariate general linear model (GLM) within SPM8 (UCL Wellcome Trust Centre for Neuroimaging, London) with a block design for navigation periods during the learning phase, where I compared those navigation trial blocks to the blocks of adjacent intertrial interval (ITI)to remove effects of slow variations in BOLD signal. There were 4 conditions of interest that characterized a learning phase navigation block: learning the location of a novel object in a novel environment, learning the location of a familiar (previously seen) object in a novel environment, learning the location of a novel object in a familiar environment, learning the location of a familiar object in a familiar environment. Within this first-level modeled we also included four retrieval phase regressors related to retrieval trials for each of the four experimental conditions. Each session included a further 6 'movement' regressors estimated during realignment. Each trial was modeled as a boxcar function lasting the length of the navigation period (i.e., the length of time the participant took to 'pick up' or 'drop' the object for that specific trial). Each condition was contrasted with the session specific ITI prior to second-level analyses. A second-level analysis was performed with these four conditions, equating to a 2x2 (Environmental Novelty x Object Novelty) factorial design.

A further subsequent memory analysis included the four encoding conditions of interest as well as four parametric modulators (one per experimental condition)

relating to the subsequent distance error for each object at retrieval. A final analysis split the encoding phase into 4 quartiles (for each of the 4 object presentations), to assess changes in novelty across encoding trials, resulting in 16 regressors (plus movement parameters). Data were high-pass filtered (cut-off period = 128 s). Based on my strong *a priori* hypotheses with respect to the involvement of medial temporal lobe (MTL) regions in novelty processing I have chosen an uncorrected statistical threshold of $P = 0.001$ and cluster threshold k=5 for the whole brain. Coordinates of brain regions are reported in MNI space. ROI analyses were conducted using 10 mm radius spherical ROIs in MarsBar (Brett et al, 2002) toolbox within SPM8 around the respective peak voxel specified in the corresponding results section.

6.3 Results

6.3.1 Behavioral Results

To assess behavioral performance, I looked at the distance error between where participants had indicated where an object was during the test phase and where it was actually located in the environment. Behaviour was generally in line with past studies using this paradigm. The average length of navigation trials was 9.04 s during the learning phase and 12.41 s during the test phase. There were no significant ($p<.05$) performance differences between memory (1/distance error) for novel versus familiar object locations ($p=.268$; $F(1,19)=1.305$), or object locations in novel or familiar environments ($p=.281$; $F(1,19)=1.229$). However, there was significantly enhanced performance ($P<.05$) for learning the location of novel versus familiar objects in novel environments ($p = .049$, $t(19) = 2.107$), similar to previous behavioural findings showing proactive interference in Experiment 1. Over the course of the experiment, participants displayed a significant linear trend ($P<.05$) of

spending less time navigating during learning (p=.024;F(1,19)=5.995;) and test trials (p=.017;F(1,19)=6.856;) in later experimental sessions (similar to experiment 1).

6.3.2 Environmental novelty during object location encoding

During the encoding phase of my navigation experiment, I compared trials in novel environments versus familiar environments (each against the ITI). I found that the left hippocampus showed a greater response (see Fig. 19) for novel versus familiar environments (peak voxel: x=-30; y=-28; z=-8; Z-score=4.41; see Fig. 19). In a subsequent ROI analysis based on the peak environmental novelty effect, the left hippocampus was shown to be selectively sensitive to environmental novelty (i.e., no object novelty effect was present; F=.906 p=.354) and no interaction between these two effects was seen (F=.093; p=.765). The right caudate extending into white matter, left cerebellum extending into midbrain, right angular gyrus, left thalamus, and right superior colliculus also showed significantly greater activity during encoding in novel versus familiar environments (see Table 4). There were no other significant activations for this contrast and for the reverse contrast (i.e., familiar environments > novel environments).

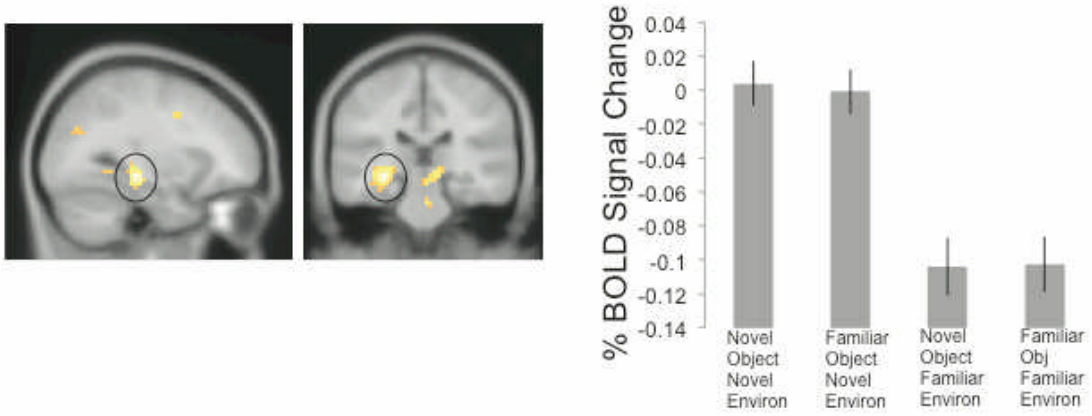

Figure 19: Environmental novelty during encoding
(Left) Sagittal and coronal images of significant left hippocampus activity (peak voxel: x=-30; y=-28;z=-8; Z-score=4.41) corresponding to environmental novelty

during the encoding phase. (Right) Difference in percent signal change against intertrial interval in left hippocampus averaged across 18 participants for navigating for all four novelty conditions during encoding phase (mean± SEM). Activations are shown at the uncorrected threshold of p<.005 for display purposes and overlaid on the MNI152 T1 image.

Region	***x***	***y***	***z***	**Z-score**
R Caudate (extending into white matter)	24	-1	16	4.56
L Cerebellum/Midbrain	-6	-37	-41	4.42
L Hippocampus	-30	-28	-8	4.41
R Angular Gyrus	27	-79	19	4,02
R Superior Colliculus	9	-28	-5	3.64
L Thalamus	-3	-13	7	3.46

Table 4. Environmental Novelty

6.3.3 Object novelty during object location encoding

I then compared learning phase trials for novel objects versus familiar objects against the ITI. I found bilateral activations spanning the fusiform gyrus and peaking in the posterior parahippocampal cortex (left peak: x=-36,y=-49;z=-11; Z-score= 3.81; right peak: x=39; y=-37; z=-11; Z-score=4.33; see Fig. 20), which significantly responded to object novelty. There were no other significant activations for this contrast and for the reverse contrast (i.e., Familiar objects > Novel objects). Both left and right fusiform gyrus/posterior parahippocampal cortex were selectively sensitive to object novelty (environmental novelty, left: F=1.045, p=.321; right: F=.107, p=.748)) and showed no interaction between the two novelty effects (left: F=1.2; p=.289; right: F=1.899; p=.186). Finally, we also observed a small cluster in the right amygdala below our significance threshold that responded to object novelty (peak: x=30; y=-1; z=-17; Z-score=3.03;; see Table 5).

Region	***x***	***y***	***z***	**Z-score**
R Parahippocampal Cortex/Fusiform Gyrus	39	-37	-11	4.33
L Parahippocampal Cortex/Fusiform Gyrus	-36	-49	-11	3.81
R Amygdala (below significance threshold)	30	-1	-17	3.03

Table 5. Object Novelty

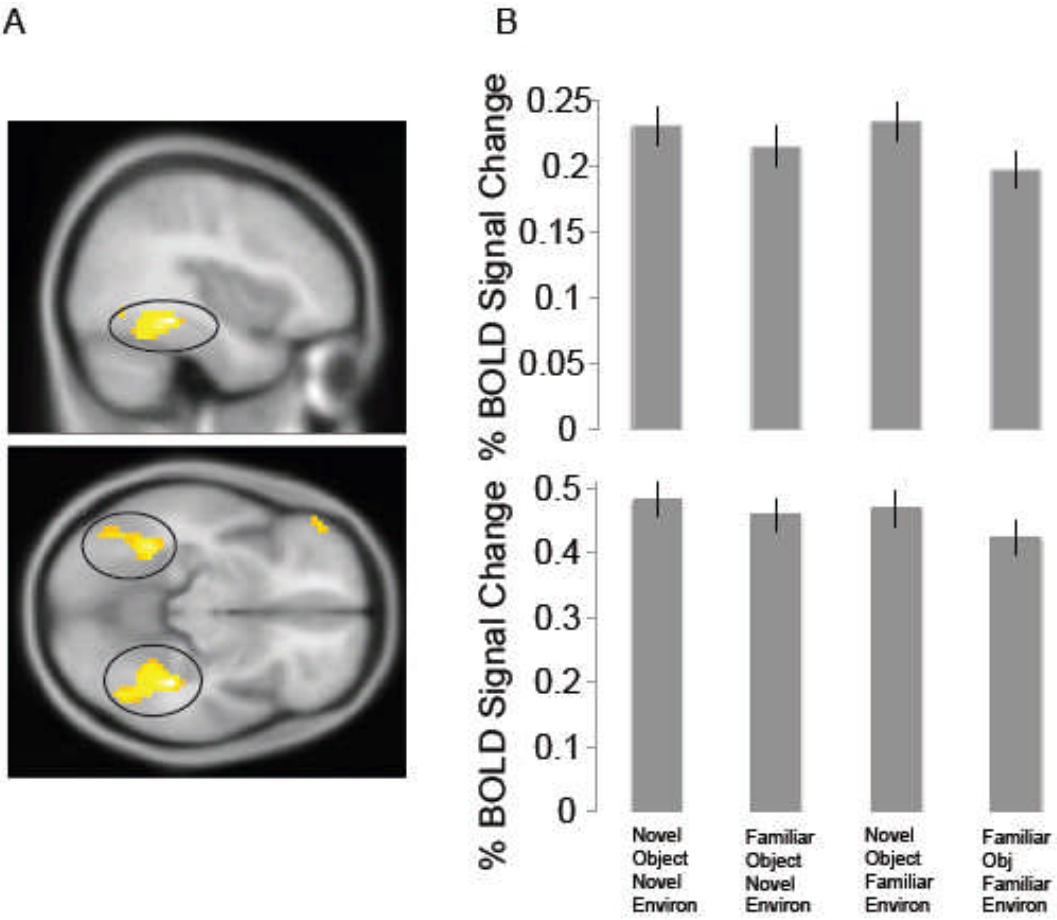

Figure 20: Object novelty activations in ventral temporal cortex during encoding

(A) Image showing significant activation for activity in right fusiform gyrus/posterior parahippocampal cortex (peak: x=39; y=-37; z=-11; Z-score=4.33;) and subthreshold activation in left fusiform gyrus/posterior parahippocampal cortex (peak: x=-36; y=-49; z=-11; Z-score=3.81;). (Top Right) Difference in percent signal change against intertrial interval in left fusiform gyrus/parahippocampal cortex and (Bottom Right) right fusiform gyrus/parahippocampal cortex averaged across 18 participants for navigating for all four novelty conditions during encoding phase (mean± SEM). Activations are shown at the uncorrected threshold of p<.005 for display purposes and overlaid on the MNI152 T1 image.

6.3.4 Subsequent memory performance effects during encoding

I also correlated subsequent distance error of memory for object locations during encoding and found that the right posterior hippocampus (peak: x=27; y=-28; z=-5;

Z-score=3.61; see Fig. 21) and right superficial amygdala/substantia innominata (peak: x=27; y=11; z=-17; Z-score=3.47; see Fig. 21), significantly corresponded to subsequent distance error significantly corresponded to subsequent distance error (collapsed across environmental and object novelty). Importantly, these performance effects were not modulated by novelty, since there was no significant difference in performance-related activity in the right superficial amygdala (Environmental Novelty: F=1.423; p=.249; Object Novelty: F=.481; p=.497;) or posterior right hippocampus (Environmental Novelty: F=2.054; p=.169; Object Novelty: F=3.368; p=.083;) for object or environmental novelty; although the hippocampus showed a modest trend towards object novelty. Although the amygdala ROI showed a marginal trend for a differential condition-specific effect with an environment x object novelty interaction, while the hippocampus did not (Amygdala: F=3.253; p=.089; Hippocampus: F=1.233; p=.281). Other regions significantly correlating with subsequent memory performance at our significance threshold were both left and right angular gyri, left thalamus/midbrain, cingulate gyrus, left and right claustrum, right ventrolateral PFC, left cerebellum/ventral temporal lobe, midbrain, right thalamus, right cerebellum, left insula, left premotor cortex and left parahippocampal cortex (see Table 6).

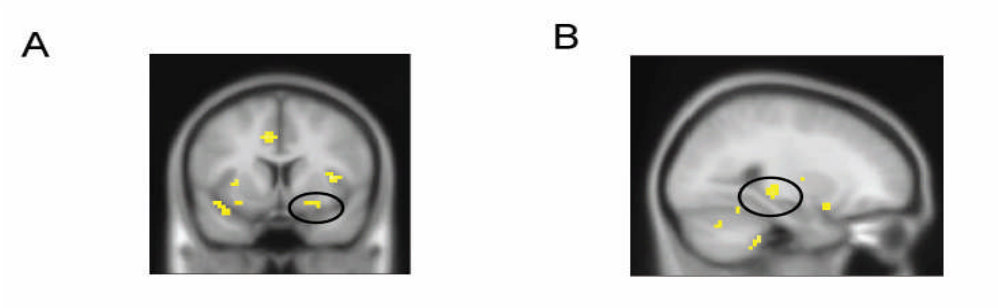

Figure 21: Subsequent memory performance effects

(A) Coronal image showing a significant increase in right superficial amygdala/substantia innominata (peak: x=27; y=11; z=-17; Z-score=3.47) activity for encoding trials that had better subsequent memory performance. (B) Sagittal

image showing a significant increase in posterior right hippocampal activity (peak: x=27; y=-28; z=-5; Z-score=3.61) for encoding trials that had better subsequent memory performance. All activations are shown at the uncorrected threshold of p<.001 and overlaid on the MNI152 T1 image.

Region	***x***	***y***	***z***	**Z-score**
L Angular Gyrus	-48	-37	19	4.32
R Angular Gyrus	63	-37	16	3.74
L Thalamus/Midbrain	-9	-28	-2	4.31
Cingulate Gyrus	-9	5	40	3.91
R Claustrum	36	8	7	3.88
L Claustrum	-30	5	1	3.75
R Ventrolateral Prefrontal Cortex	51	38	1	3.82
L Cerebellum/Ventral Temporal Lobe	-30	-34	-29	3.80
Midbrain	10	-24	-26	3.76
R Thalamus	9	-28	1	3.75
R Cerebellum	27	-37	-41	3.67
R Hippocampus	27	-28	-5	3.61
L Insula	-45	5	-17	3.51
R Substantia Innominata/Superficial Amygdala	27	11	-17	3.47
L Premotor Cortex	-9	-7	61	3.33
L Parahippocampal Cortex	-27	-43	-17	3.23

Table 6. Subsequent Memory Performance during Encoding

6.3.5 *Temporal effects of object and environmental novelty during encoding*

Lastly, to further dissociate between MTL structures, particularly to see if the amygdala object novelty effect was temporally modulated, I investigated how the above environmental and object novelty effects changed across time (across the learning phase). I split learning phases into four quartiles (matching the four repetitions of object location encoding during the learning phase) and assessed both environmental and object novelty across these quartiles. Searching for a linear decrease of environmental novelty from quartiles 1-4 failed to reveal any significant regions in the MTL or neocortex. Conversely, a linear decrease in object novelty across time was seen in the left amygdala (x=-27; y=-1; z=-14; Z-score=3.65; see Fig. 22) and left posterior parahippocampal cortex (x=-36; y=-37; z=-17; Z-score=3.87).

These analyses suggest our original environmental/object novelty effects may further dissociate in terms of how rapidly they attenuate across time. I examined the effect of initial object novelty in the first quartile of the encoding phase (i.e. first presentation of novel objects versus familiar objects) across the whole brain, since the novelty effect in the amygdala was highest in the first quartile (see Fig. 22A). I found significant bilateral amygdala activations for initial object novelty (left peak: x=-21; y=-7; z=-14; Z-score=3.78; right peak: x=21;y=-4;z=-14; Z-score=3.39; Fig. 22C), second only to the right fusiform gyrus in significance across the whole brain. However, I also found that activity in the amygdala increased with familiarity after many presentations (see Fig 22B), particularly when it is seen in a new location in a familiar environment. Thus, while there is a strong relationship of amygdala activity to the novelty of an object or object-location in the first two trials of a session containing that object, its increase over the last two trials of the session indicates the presence of more than a simple novelty response.

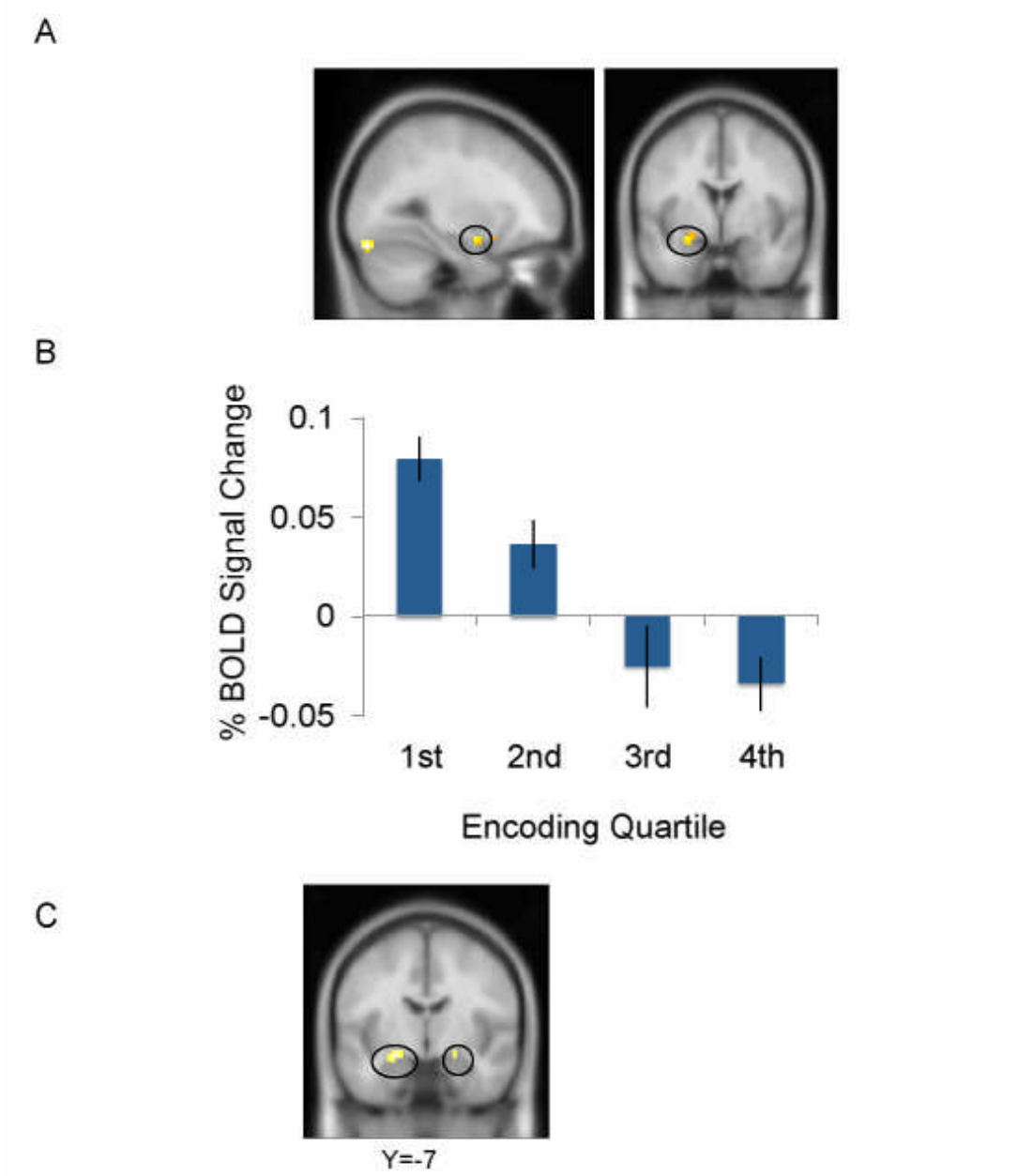

Figure 22: Object novelty processing and the amygdala
(A) Sagittal and coronal images of significant left amygdala activity (peak: x=-27; y=-1;z=-14; Z-score=3.65;) corresponding to a linear decrease in activity for object novelty (novel versus familiar objects) over the course of the learning phase (B) Charts difference in percent signal change in the left amygdala for novel versus familiar objects split across encoding phase by quartile. (C) Coronal image of significant bilateral amygdala activity (left peak: x=-21; y=-7; z=-14; Z-score=3.78; right peak: x=21;y=-4;z=-14; Z-score=3.39) for trials where a novel object is presented for the first time during encoding (1st Quartile) versus a familiar object being presented for the first time during the encoding phase. All activations are shown at the uncorrected threshold of p<.001 and overlaid on the MNI152 T1 image for display purposes.

6.4 Discussion

I investigated environmental and object novelty during a spatial navigation task. I was interested in determining whether different regions corresponded to different forms of novelty. During spatial memory encoding, I found that environmental novelty was associated with activation of the left hippocampus (see Fig. 19) and the right caudate. Object novelty was reflected in activation of both left and right fusiform gyrus/parahippocampal cortex (see Fig. 20). Notably, activity in the right posterior hippocampus and amygdala correlated with subsequent memory performance (see Fig. 21) and was independent of novelty. I also found that the amygdala was strongly activated for the first presentation of an object, regardless of environment (see Fig. 22).

My finding of hippocampal involvement in environmental rather than object novelty during spatial learning parallels previous findings in rodents (Save et al. 1992a; Save et al. 1992b; Moses et al. 2002; Lee et al. 2005; Moses et al. 2005). It also supports the proposed role of the hippocampus as a contextual novelty detector (Kumaran et al, 2006; Good et al. 2007) that does not exhibit a generalized response to all novel stimuli (cf., Sokolov, 1963). It is interesting to note that previous fMRI findings have implicated the hippocampus and caudate in the disambiguation of overlapping routes (Brown et al. 2012; Brown and Stern 2013). Finding hippocampal and caudate activations associated with environmental novelty may relate to how interactions between the hippocampus and striatum guide learning during exploration (Pennartz et al. 2011; van der Meer et al. 2012).

My observation that ventral temporal cortex, posterior parahippocampal cortex/fusiform gyrus, represented object novelty during learning is in line with previous studies of object adaptation and novelty detection (Ewbank et al. 2005;

Preston et al. 2010; Howard et al. 2012). Yet, the finding that parahippocampal cortex encodes novel objects, instead of novel environments during a navigation task, adds a new twist to the hypothesized role of parahippocampal cortex in processing spatial layout (Owen et al. 1996; Bohbot et al. 1998). Although my results resemble data from associative novelty tasks (Kumaran et al. 2006; Kohler et al. 2005), participants in this task are binding egocentric viewpoints of an object location within an environment to gain an allocentric representation of location. As a result, detecting object-location novelty rather than just object novelty is slightly different than mismatch detection and associative novelty tasks. This element of the experiment may be the underlying cause for the activation of parahippocampal cortex, as opposed to a perirhinal cortex (PrC) activation hypothesized by previous models of item versus context memory (Eichenbaum et al. 2007; Diana et al. 2007; Ranganath & Ritchey 2012). Future research will investigate how and at what time scale, novel content versus contexts are both implicitly encoded and explicitly recalled in the medial temporal lobe.

Although the amygdala is most commonly activated in fMRI paradigms using affective and reward-related stimuli (Phelps, 2006; Seymour & Dolan 2008; Adolphs, 2010), my findings are in accordance with previous results from a rodent study associating amygdala lesions to impaired object novelty detection (Moses et al. 2002, 2005;) and closely parallel human intracranial recordings showing amygdala and sometimes anterior hippocampal responses to novel or surprising events (Halgren et al. 1980; Knight 1996; Fried et al. 1997; Rutishauser et al. 2010). Furthermore, our amygdala results are localized mainly to the dorsal amygdala extending into the sublenticular substantia innominata, an area responsible for processing surprise omissions (i.e. surprise appearances and disappearances of

objects in an environment) in associative learning paradigms (Holland et al. 2006; for review see Holland and Gallagher 1994). Human fMRI studies focusing on face perception and other animate items (Blackford et al. 2010; Balderston et al. 2011; Mormann et al, 2011) have also implicated the amygdala. There is now an emerging fMRI literature on the amygdala related to arousal (Thoresen et al. 2011), perceptual insight (Ludmer et al. 2011), and vividness (Kensinger et al. 2011), supported by studies recording from the rodent amygdala that have investigated its responses to complex visual stimuli (O'Keefe et al. 1969; Bagshaw et al. 1972; Halgren et al. 1978). Taking these studies into consideration, along with our own finding, we suggest that the human amygdala might code the novel content within a given context, potentially independent of specific affective or reward valance. Nonetheless, it is still unclear why the amygdala increases in activity after several presentations in an environment, but we note a similar finding in an incidental learning study Manelis and colleagues (2013) in which right amygdala activation first reflects novel object locations compared to the second and third repetition, but then increased with subsequent presentations (i.e. as the object location becomes more and more 'familiar').

When correlating each encoding trial with subsequent memory performance, we found a posterior right hippocampal activation, matching past studies demonstrating the importance of the posterior right hippocampus and spatial memory performance (Abrahams et al. 1997; Bohbot et al. 1998; Maguire et al. 1998; Spiers et al. 2001; Doeller et al. 2008; Igloi et al. 2010). We also found activation in the right amygdala/substantia innomenata, which is consistent with correlations found between superficial amygdala/substantia innominata volume and memory performance in older adults (George et al. 2011). Our activation of the right

substantia innominata is further evidence of the importance of the nucleus basalis in memory performance. Furthermore, we found that hippocampus and amygdala activations correlated with memory performance independent of object and environmental novelty. Thus, the amygdala and hippocampus both appear to show a generalized contribution to subsequent memory performance and a condition-specific involvement according to object and environmental novelty (see also, Rutishauser et al. 2010; Staresina et al. 2011; Bird et al. 2012; Kumaran et al. 2012).

6.5 Conclusions

I employed a virtual spatial navigation paradigm with high ecological validity to assess how the human brain learns about novel environments and content (object-locations). I found evidence of region-specific processing of novelty within the MTL, where hippocampal activations corresponded to environmental novelty, while fusiform gyrus/parahippocampal activations corresponded to the locations of novel objects. My results suggest that detection of novel stimuli is region-specific in the MTL, while subsequent mnemonic performance related activity in the amygdala and hippocampus is independent of stimulus novelty.

Chapter 7

*Experiment 4: Resting state fMRI predictors of spatial memory performance at 3T and 7T.**

*This work is partly derived from work presented in R Kaplan, WM Luh, C Doeller, N Burgess, P Bandettini "A 7T resting state fMRI study of MTL-Neocortical Connectivity Changes after Spatial Learning" *Organization for Human Brain Mapping 2012*; and R Kaplan, C Doeller, P Bandettini, & N Burgess "Subsequent memory and the maintenance of spatial representations over different time scales" *Society for Neuroscience 2011*

Precis

A prominent finding in rodent spatial exploration is that endogenous hippocampal activity (detailed in Chapter 2) reflects previously travelled spatial trajectories, or how future trajectories will be encoded. Human fMRI research has built on these findings by showing that hippocampal BOLD connectivity with task-relevant regions during intervening rest/endogenous periods predicts individual memory performance (detailed in Chapter 2). I wanted to push the link between findings relating endogenous activity to memory formation further by determining whether the endogenous activity of default mode network structures, such as the hippocampus, mPFC and posterior cingulate cortex, that are prominently active during navigation tasks, is also involved in memory formation. I was interested in using 3T to determine interregional (e.g. mPFC-hippocampal, hippocampal-parahippocampal cortex) resting-state functional connectivity changes during memory tasks, to see if it might relate to an individual's memory performance. I then wanted to use high-field 7T imaging to find whether hippocampal subregion-neocortical (e.g. CA1-mPFC, subiculum-retrosplenial cortex) resting-state functional connectivity changes might predict individual memory performance.

7.1 Introduction

The "default mode network" (DMN) is a common source of deactivation when comparing working memory and attention-related task activity to 'task-free' baseline periods in neuroimaging tasks, yet the behavioural significance of this core resting state network is unknown. Notably, past work observed that the default network shows a striking overlap with areas active during spatial navigation, autobiographical and episodic memory tasks (Buckner & Carroll 2007; Hassabis &

Maguire 2007). Evidence from rodent electrophysiology shows that connectivity between the parietal and frontal midline with the hippocampal formation might be important for memory consolidation (Kesner 2000; Wierzynski et al. 2009; for review see Wang & Morris 2010). Human sleep research has also implicated these areas in long-term memory consolidation (see Gais et al. 2007). Recently, studies have shown that post-learning offline activity in task dependent regions can predict individual memory performance (Peigneux et al. 2006; Tambini et al. 2010; van Kesteren et al. 2010; Wegman & Janzen. 2011). Furthermore, ongoing hippocampal activity prior to memory encoding has also been implicated in predicting subsequent performance (Wig et al. 2008; Wang et al. 2010). Interestingly, classical memory consolidation theories (Nadel et al. 2000; Frankland & Bontempi 2005; Squire et al. 1984; Wang & Morris 2010) have focused on the time scale of hours, days, weeks, or years, but the temporal dynamics of memory formation within a 30-min session are unclear. Hence, I was interested in how offline connectivity across the different time scales immediately surrounding learning might relate to consolidation, and whether activity within default network hubs could reflect differential connectivity depending on the time point within learning (i.e. determine whether endogenous fMRI functional connectivity patterns vary with learning).

Using both standard 3T and ultra-high field 7T functional magnetic resonance imaging, I examined data from offline periods (pre-learning rest, inter-trial interval or 'ITI' during encoding periods, and post-learning rest) during the object-location task used in Chapters 4, 5, and 6. For the 3T experiment, participants underwent a continuous fMRI scan with five stages, pre-learning rest (4 mins), spatial learning 1 (6 mins), post-learning rest 1 (4 mins), spatial learning 2 (6 mins) and post-learning rest 2 (4 mins). For the 7T experiment, the five stages were in

separate scans with the same structure alternating between 8 minute rest scans and approximately 9 minute spatial learning scans. For similar paradigms see (Tambini et al. 2010; Wegman & Janzen 2011). Afterwards, for both of these experiments, a test of object location distance error was used as a parametric measure of individual performance.

For the 3T experiment, three default network hubs were implemented as seed regions, the medial prefrontal cortex (mPFC), the left and right mid-hippocampus, and I looked at what connectivity across the whole brain might predict subsequent memory performance. I focused on the mPFC and hippocampus, because of their highly specific role in the rodent memory consolidation literature (Frankland & Bontempi 2005; Wang & Morris 2010). I specifically chose mid-hippocampal regions because they were in close proximity to areas that showed significant activation during encoding in Experiment 1, and its rodent analogue is a key region in rodent spatial cognition (Bast et al. 2006). I also attempted to examine similar changes in endogenous activity with high-resolution 7T, and examine different neocortical functional connectivity of substructures within the hippocampal formation. I was interested whether default mode network (DMN) and hippocampal formation areas that showed post-learning connectivity also displayed connectivity prior to learning that predicted individual memory performance, and whether this connectivity was with the same regions. I additionally investigated performance-modulated activity prior to stimulus presentation in between individual spatial learning trials to see whether such offline activity occurred within the default mode and spatial memory networks.

In line with past studies, I predicted that there would be post-learning induced connectivity between the hippocampus and other navigation task-relevant

regions outside the cortical midline that correlated with performance (Tambini et al. 2010; van Kesteren et al. 2009; Wegman & Janzen 2011). Conversely, I predicted that during pre-learning rest, we would observe subsequent performance related hippocampal activity (Wig et al. 2008; Wang et al, 2011) but not resting-state correlations between the hippocampus and other areas observed post-learning (Tambini et al. 2010; Wegman & Janzen 2011). Based on past literature, the sustained nature of this activity should also cause it to show significant overlap with performance-modulated activations during the ITI (Fernández et al. 1999a; Peigneux et al. 2006; Wig et al. 2008; Olsen et al. 2009; Park & Rugg 2010; Ben-Yakov & Dudai 2011). In sum, I was interested in finding evidence relating endogenous DMN fluctuations to subsequent memory retrieval performance.

7.2 Methods

The data from Experimental task 1 were taken from offline periods during and flanking the fMRI experiment from Chapters 4, 5, and 6 (5 min taskless periods surrounding the object location sessions). Therefore, the information about participants, stimuli, task, data acquisition, and some preprocessing steps are the same as in Chapters 4, 5, and 6. The aforementioned details in the methods will be briefly summarized here.

7.2.1 Participants

For experimental task 1, fourteen right-handed male participants (mean age= 23.1 yrs., SD= 5.4 yrs., range 18-35) gave written consent and were compensated for performing the experimental task, as approved by the local Research Ethics Committee.

In experimental task 2, eight right-handed male participants (mean age=28.4; SD=6.9 yrs; range 22-41 yrs). Before scanning, participants received information about the procedure of the experiment and gave their written informed consent to participate. The experiment was conducted in accordance with the Institutional Review Board of the National Institutes of Mental Health (Bethesda, Maryland, United States).

For both tasks, all participants were right-handed with normal or corrected-to-normal vision and reported to be in good health with no prior history of neurological disease.

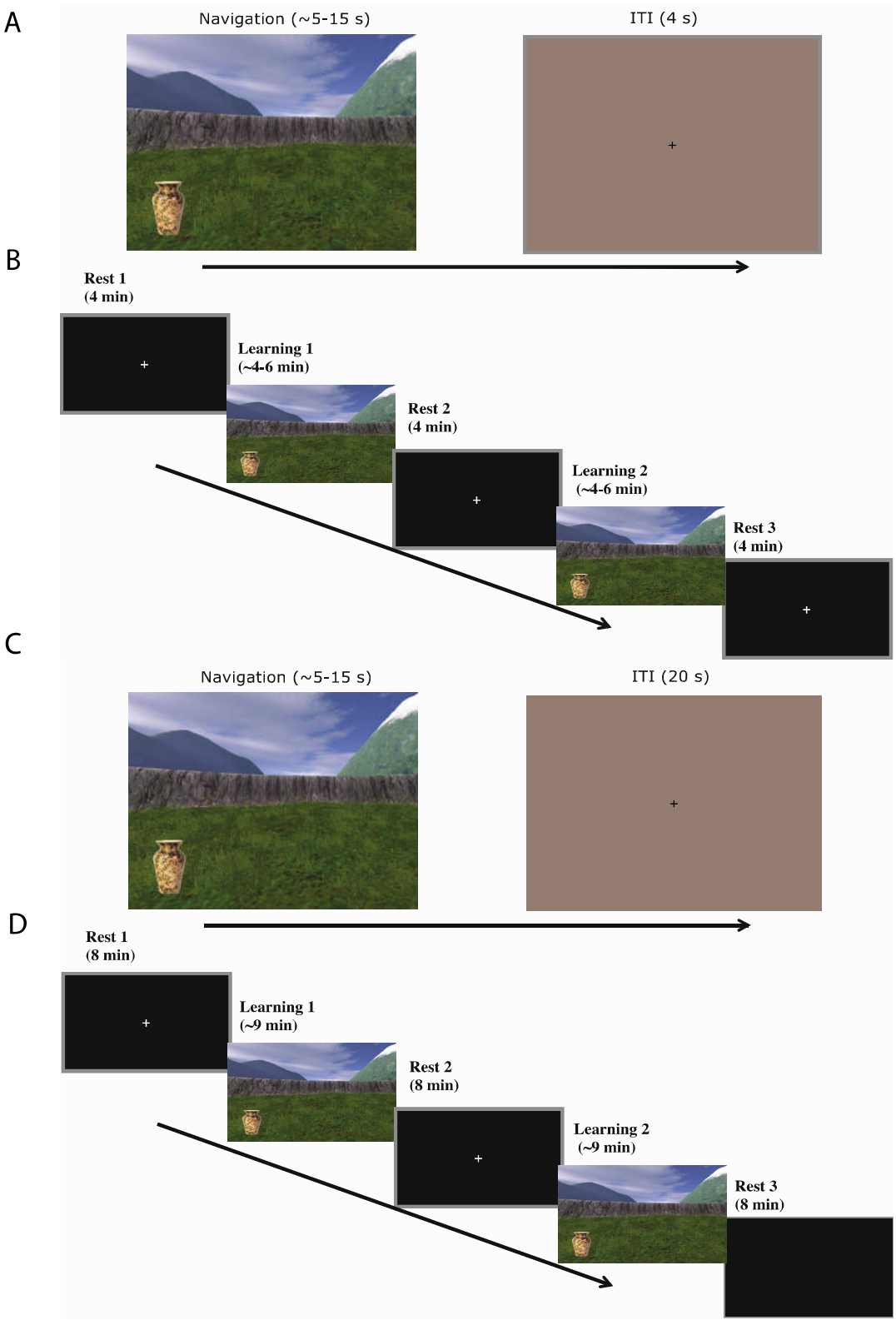

Fig. 23: Experimental Design

A. Participants performed a spatial memory task where they navigated through a virtual environment by pressing a button box. Subjects performed eighteen navigation trials per session in which six objects were found three times each with a 4-s ITI period. B. Participants either navigated and learned object locations for two

sessions or viewed a crosshair during 3 interleaved rest sessions for a total of 5 scanned subsections (total continuous acquisition ~ 25 min).. C. In the 7T, participants performed the same memory task with the same setup, however there was a 20-s ITI period. D. In the 7T, participants either navigated and learned object locations for two sessions or viewed a crosshair during 5 separate sessions. For both 3T and 7T tasks, subjects were tested on object location for the first learning session and then the second learning session after fMRI scanning (usually conducted during the MPRAGE structural afterwards.)

7.2.2 *Virtual Reality Environment:*

UnrealEngine2 Runtime software (Epic Games) was used to present a first-person perspective viewpoint of a grassy plane surrounded by a circular cliff with a background of mountains, clouds, and the sun. In the environment, background cues were projected at infinity, to provide orientation but not location within the arena. Participants moved the viewpoint by using their right hand to press keys to move forward, or turn left or right. Virtual heading and locations were recorded every 25 ms.

Experimental Task 1

The experiment was composed of five phases within an approximately 25 minute continuous fMRI scan (see Fig.23). During the scan, participants either were viewing a white crosshair overlaid on a black background for four straight minutes (three runs), or did a spatial learning task in a virtual environment (two runs). In the spatial learning task, participants either navigated in a self-paced manner through a virtual environment learning an object location or looked at a black crosshair overlaid on a grey background during a 4-s inter-trial interval intended to account for the timescale of the BOLD signal. In the spatial memory experiment, participants had two different spatial learning period sessions (~ 6 mins per session), which were flanked by the (4 mins) resting scans.

During the spatial learning component, participants were instructed that they were going to navigate through a virtual environment over multiple sessions using a button box, and that they would have to pick up several different objects (six) in the environment, three times each. The order of trials was randomized but (unknown to subjects) separated into three mini-blocks. Object location never changed within a session. After fMRI scanning, participants had separate test sessions (i.e. first test for first learning session, second test for second learning session) for each respective learning session to gauge subsequent performance, where they thought the object had been located and press a button.

The two spatial learning sessions were conducted in the circle mountain environment used in the MEG experiment from Chapters 4, 5, and 6.

Experimental Task 2

The experiment was composed of five scanning runs, including three 8 minute resting state periods with eyes open fixation and two approximately 9 minute self-paced spatial learning sessions. During these different runs, like in experimental task 1, participants either navigated in a self-paced manner through a virtual environment while learning the locations of different objects or watched a black crosshair overlaid on a grey background during a 20-s inter-trial interval intended to looked for endogenous fluctuations in the BOLD signal. In the spatial memory experiment, participants had two different spatial learning period sessions (~9 mins per run), which were flanked by 8 minute resting state runs. Otherwise, the spatial learning component of this task was the same as experimental task 1.

7.2.3 *fMRI Acquisition*

Experimental Task 1

Functional images were acquired on a 3T Siemens Allegra scanner. Blood oxygenation level dependent (BOLD) T2*-weighted functional images were acquired using a gradient-echo EPI pulse sequence acquired obliquely at -45 degrees with the following parameters; repetition time 2880 ms; echo time, 30 ms; flip angle, 90 degrees; slice thickness, 2 mm; interslice gap, 1mm; in-plane resolution, 3 X 3 mm; field of view, 64x72 mm^2; 48 slices per volume. A field-map using a double echo FLASH sequence was recorded for distortion correction of the acquired EPI (Weiskopf et al. 2006). After the functional scans, a T1-weighted 3D MDEFT structural image (1 mm^3 resolution) was acquired to co-register and display the functional data.

Experimental Task 2

Functional images were acquired on a Siemens 7T scanner. BOLD T2*-weighted functional images were acquired using a gradient-echo EPI pulse sequence acquired obliquely at ~-10 degrees with the following parameters; repetition time 2500 ms; flip angle, 90 degrees; slice thickness, 1.8 mm; in-plane resolution; 1.8 x 1.8 mm; 64 slices per volume. After the functional scans, a T1-weighted MPRAGE structural image (1 mm^3 resolution) was acquired to co-register the functional data.

7.2.4 fMRI Preprocessing

All preprocessing and analyses were performed with SPM8 (www.fil.ion.ucl.ac.uk/spm). All individual structural images underwent segmentation (into grey matter, white matter and cerebro-spinal fluid), bias correction and spatial normalization to the MNI template using 'unified segmentation' (Ashburner & Friston 2005). Using the Montreal Neurological Institute (MNI) template brain, the first six EPI volumes were discarded to allow for T1 equilibration. EPI images had distortion

correction and were realigned spatially to the time series' first image based on the collected field map [Hutton et al, 2002] and the interaction of motion and distortion using the Unwarp routines in SPM (Andersson et al, 2001; Ashburner & Friston 2005). Functional images were normalized based on the spatial parameters derived from the normalization of their structural images. Normalized EPI images were spatially smoothed with an 8 mm isotropic FWHM Gaussian kernel. All coordinates are in MNI space.

7.2.5 fMRI Data Analysis

Statistical analyses were performed using a univariate general linear model (GLM) with a rapid event-related experimental design. Data was high pass filtered at 128-s. The conditions of interest, the 4-s Inter-Trial Interval (ITI), was modeled as a boxcar function (duration of 4-s) and convolved with the canonical hemodynamic response function (HRF) to create a regressor of interest. Subject-specific beta values (parameter estimates) were calculated for each voxel and the respective condition images (ITI) were entered into one-sample t-tests in a second-level random-effects analysis. In a second analysis across subjects, the ITI images were correlated with each subjects' mean object replacement performance (mean distance error in virtual meters) during the test phase. Based on our strong a priori hypothesis about the default network hubs, we chose the threshold of $p<.005$ (uncorrected for multiple comparisons) with an extent threshold of 5 voxels.

7.2.6 Resting State Analyses

Data were realigned and preprocessed within SPM8. Data was then split into the three separated 85 volume resting state sessions and denoised using FSL (www.fmrib.ox.ac.uk/fsl) Multivariate Exploratory Linear Optimized Decomposition into Independent Components (Beckmann et al, 2005). Artifactual components as

determined by each datasets' time course and spatial maps were then removed. Data was then bandpass filtered from 0.01 to 0.1 Hz within the AFNI software package (Cox 1996) and each participant's two post-learning rest trials were concatenated into one post-learning run. Connectivity measures were calculated within AFNI using 3dGroupInCorr, which calculates the connectivity (arctanh) between a specified seed region and all other voxels in the brain. A Z-score was calculated of the t-statistic of the differences between the 2 slopes (covariate subject distance error versus whole brain voxel correlation to specified seed voxels with a 5 mm radius). The specified seed voxels were in the medial prefrontal cortex (x=0; y=48; z=2), left mid-hippocampus (x=-28, y=-26, z=-10) and right mid-hippocampus for (x=28, y=-26, z=-10). Seed regions were selected based on their location within default network hubs that showed connectivity with each other across all 3 rest periods and specifically in the case of the hippocampal seed regions for their activation in the spatial memory task. Based on our hypothesis of learning correlated changes within the default network, we chose the significance threshold of $p<.005$ uncorrected.

7.3 Results

These analyses were informed by data from Experiment 1 showing bilateral midline hippocampal activity during an active behaviour (movement initiation during virtual navigation) and correlated with individual spatial memory performance (average distance error).

7.3.1 Post-Learning Resting State Connectivity

We investigated post-learning connectivity changes between the three hubs of the default network, the medial prefrontal cortex, the left hippocampus, and right

hippocampus and other brain areas that correlated with performance, which was an increase in individual subsequent spatial replacement accuracy (reduced mean distance error). Marginally significant endogenous correlations between DMN hubs and other brain regions that predicted spatial memory performance ($p<.005$, Z-score=2.807) were found between the left hippocampus and other brain regions, but not in the other two seed regions. Post-learning, left mid-hippocampal resting state connectivity with the right parahippocampal cortex/subiculum (peak voxel: x=20; -26; -12; Z-score= 2.92; See Figure 24), left posterior parahippocampus (peak voxel: x=-18;y=-44;z=-14; Z-t score= 3.74; See Figure 24), right dorsolateral prefrontal cortex (peak voxel: x=-18; y=-38; z=34; Z-score= 3.15; see Figure 24), and right temporal pole (peak voxel: x= 58; y= 4; z=-14; Z-score= 3.13) predicted subsequent memory performance. Marginally significant correlations also extended into parts of the right hippocampal formation and parahippocampus.

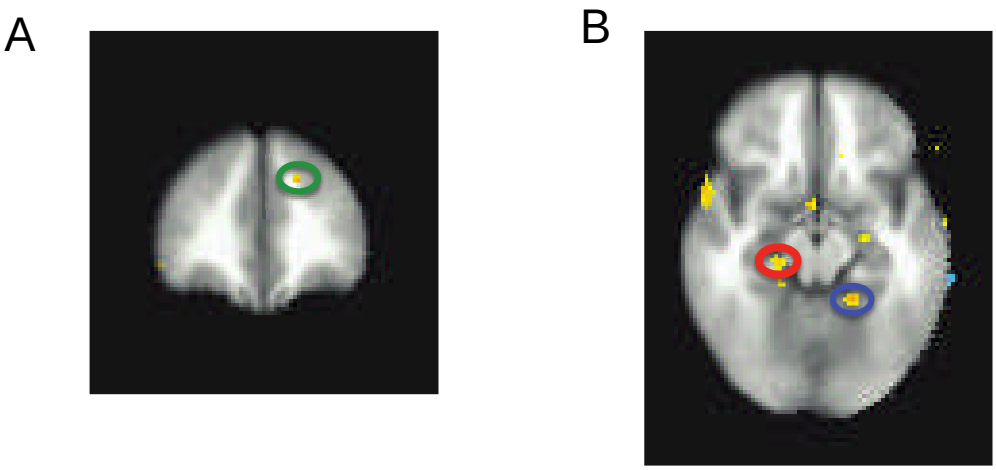

Fig 24: Post-Learning Left Hippocampal Resting Connectivity

A. Axial and coronal images showing that the Right Parahippocampal Cortex (in red; peak: x=20; -26; -12; Z-score= 2.92), left PPA (in blue; peak: x=-18;y=-44;z=-14; Z-score= 3.74), and DLPFC (in green; peak: x=-18;y=-38;z=34; Z-t score= 3.15), that have significant ($p<.005$) post-learning resting state connectivity with the Left Midline Hippocampus seed region (peak x=-28 ,y=-26 z= -10; not shown) that correlates with individual subsequent memory performance. Shown thresholded at $p<.01$ for display purposes. Activations are overlaid on a MNI152 T1 image. B. Z-

scores for each participants' for both post-learning and pre-learning left hippocampal midline resting state correlations in the Right Parahippocampal Cortex, Left PPA, and Right DLPFC peak voxels against their average replacement accuracy in virtual meters.

7.3.2 Pre-Learning Resting State Connectivity

I determined if the same or any new areas showed increased connectivity with the left hippocampus that correlated with performance (mean distance error). No significant increases were found in the main regions where post-learning increases were observed. The strongest increased connectivity in default network hubs was observed with the right dorsomedial prefrontal cortex (peak voxel: x=10, y=64, z=10; Z-score=3.13; See Figure 25A) and right anterior medial temporal lobe (peak voxel: x= 22;y= -10; z= -28; Z-score=3.14; see Figure 25A), but also there were marginal correlations in other areas including the right rostral orbitofrontal cortex, left cerebellum, and left inferior parietal cortex.

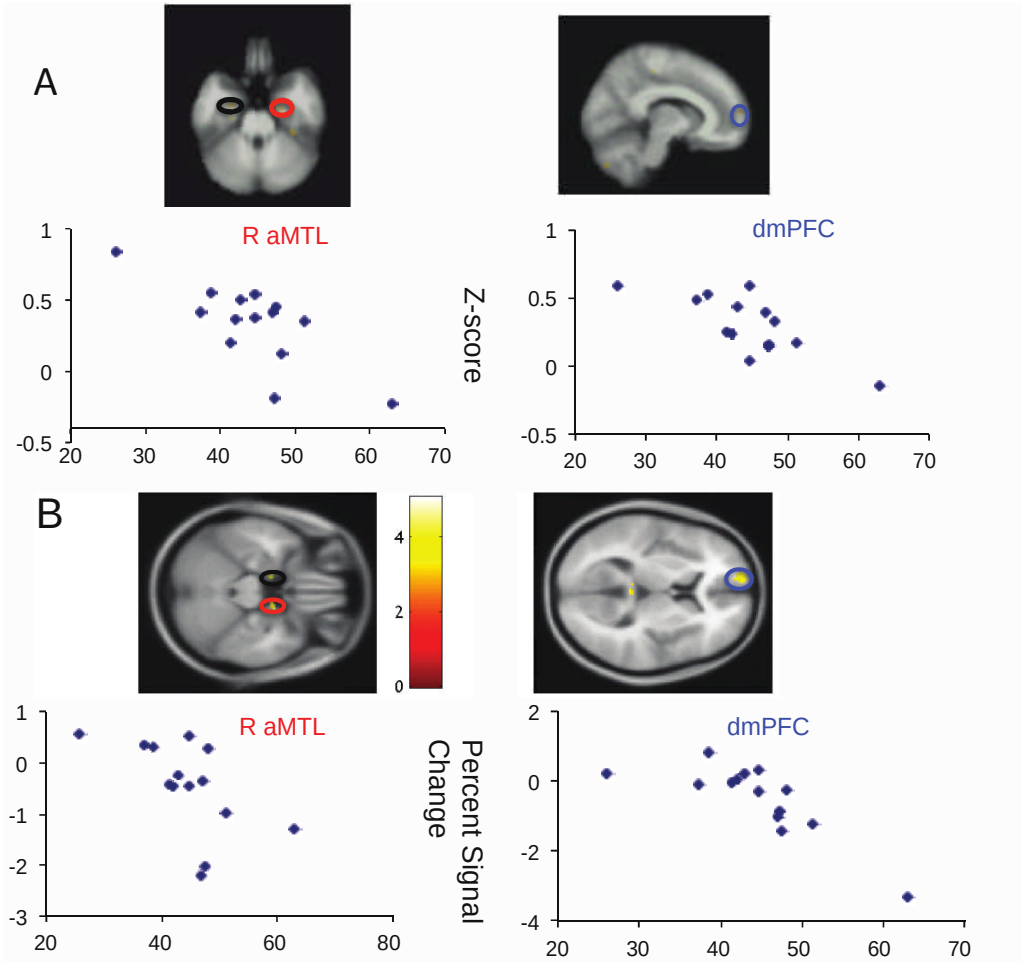

Fig 25: Pre-learning rest and ITI performance correlates
A. Axial and sagittal image showing left midline hippocampal seed region (not shown) pre-learning rest state correlation with anterior Medial Temporal Lobe (right peak in red;x= 22;y= -10; z= -28; Z-score=3.14) and mPFC (peak in blue; x=10, y=64, z=10; Z-score=3.13) that significantly correlates with performance (thresholded at p<.005).. Activations are overlaid on a MNI152 T1 image. B. Axial images showing the correlation of left and right anterior MTL (peak in black; x=-12 y= -4; z=-24 ; Z-score= 3.00; peak in red; x= 12; y= -4; z= -24; Z-score= 3.25 ; thresholded at p<.005), retrosplenial cortex (peak not shown), and dmPFC (blue peak; x= 12;y= 62;z= 8; Z-score=3.26; thresholded at p<.005) Inter-Trial Interval Activity with each participant's mean performance. Activations are overlaid on a MNI152 T1 image.

7.3.3 Inter-Trial Interval Performance Correlation

As a follow-up to the resting state connectivity analyses, we correlated each participant's average subsequent accuracy (mean distance error) with activity during the 4-s ITI at the less stringent significance threshold of p<.005 uncorrected: t(12)=3.05. The key nodes showing connectivity in pre-learning rest were also found

to have activity that correlated with performance during ITI. We found that increased activity in the main nodes of the default network, medial prefrontal cortex (peak voxel: x= 12; y= 62; z= 8; Z-score=3.26), bilateral anterior medial temporal lobe (left peak: x=12; y=-4; z=-24; Z-score= 3.00; right peak: x=-12; y=-4; z=-24; Z-score=3.25), and also retrosplenial cortex (peak voxel: x=-4, y=-38, z=12; Z-score=3.15) was associated with better performance (see Figure 25B). Increased activity in the left rostral orbitofrontal cortex, cingulate gyrus, bilateral middle temporal gyrus, and in the vicinity of the caudate relative to navigation trials was also observed.

7.3.4 7T Results

7.3.4.1 Navigation

Physiological noise in seven out of eight participants made the data impossible to analyse, so I was unable to make any group-level inferences on the effect of performance or task versus baseline. In one subject, the brain network commonly associated with spatial navigation versus baseline trials was clearly activated without smoothing at single-participant significance threshold of $p<.001$ uncorrected (See Fig 26). In the medial temporal lobe, activations stretched from bilateral posterior parahippocampal cortex into the entorhinal cortex and also into the posterior hippocampus.

7.3.4.2 Resting State Networks

Despite the large amount of noise in the signal with the 7T scanner, we were able to extract the DMN with ICA denoising. However, without accurate task-related activation in seven out of eight participants, we did not have task-relevant regions to compare to or a sufficient signal to noise ratio to make group-level inferences. If

physiological measures such as respiration and heart rate were used as regressors, inferences on the resting-state data potentially could have been made.

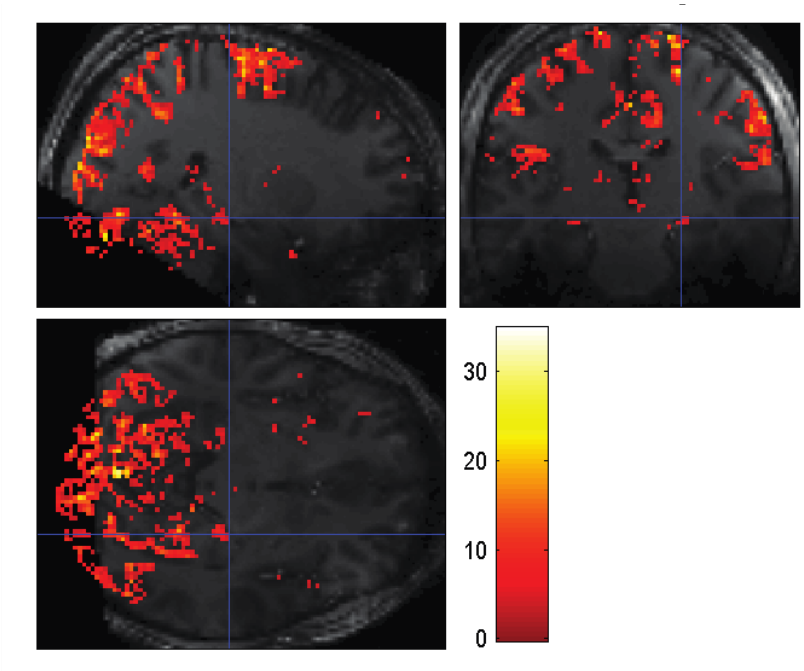

Figure 26: Virtual navigation activity at 7T

Shows unsmoothed task-related activation (navigation versus ITI) for a single participant from the 7T task. Note activations in the navigation network including the hippocampus. Data is overlaid on the participant's structural and is displayed at the significance threshold of p<.001 uncorrected.

7.4 Discussion

Out of three default network seed regions, I found that only endogenous correlations between the left mid-hippocampus (the area that showed the strongest correlation during our spatial location encoding task) and neocortex predicted individual memory performance after spatial learning and that these hippocampal correlations that predicted performance were highest with right parahippocampal cortex/subiculum, dlPFC and more lateral neocortical areas of the default network. This left seed region also showed increased performance modulated connectivity, primarily with cortical midline and aMTL areas that are part of the default network. Furthermore, the cortical midline and aMTL areas that showed the strongest pre-

learning resting state connectivity with the left hippocampus also showed the most performance predictive activity during the ITI of the encoding period.

Post-learning correlations with the left hippocampus and the neocortex predicted individual spatial memory performance. The finding that only the left and not right hippocampus or medial prefrontal cortex displayed learning induced connectivity changes with the neocortex may relate to the stronger subsequent memory performance effect in the left hippocampus from the spatial memory task (Kaplan et al. 2012). Consequently, these effects might be a power confound, since there is more power to detect effects with the left hippocampus due to greater variance in activity. The increased connectivity between the left hippocampus and bilateral parahippocampal cortices demonstrates interhemispheric connectivity between the medial temporal lobes after spatial learning, shown in previous work (Wegman & Janzen 2011). Notably, the increase in performance correlated connectivity with the temporal pole might be related to the key role that it is thought to play in episodic memory retrieval (Maguire & Mummery, 1999). Although I expected more changes in connectivity that predicted memory performance along the cortical midline, my data might indicate a lateral shift within the default network from hippocampal-cortical midline connectivity being important prior to learning, to hippocampal-lateral parietal/frontal connectivity being important after learning. This midline to lateral shift to memory-retrieval regions would be in line with previous work on human memory consolidation (Nadel et al. 2000; Takashima et al. 2006; Takashima et al. 2009).

Finding hippocampal-prefrontal connectivity that differed in spatial topography (i.e different areas of the hippocampus and prefrontal cortex) in the pre-learning rest period, might signal a different role for the hippocampal-neocortical

dialogue prior to learning. The importance of ongoing activity in cortical midline structures of the mPFC is evident by its robust activity during rest, but also in its activity during cognitive tasks like autobiographical memory, spatial navigation, and future planning (Hassabis & Maguire 2007; Buckner et al. 2008). Furthermore, the interhemispheric pre-learning resting state connectivity between anterior MTL regions that correlated with memory performance is in line with previous work investigating its importance for performance in a subsequent free recall task (Wang et al. 2010). Interestingly hippocampal connectivity with parietal areas has been shown to be important for human memory encoding (Wagner et al. 2005) and rodent navigation (Kesner 2000).

Performance correlated activity during the ITI showed overlap with the main areas regions that displayed left hippocampal connectivity during pre-learning rest. The anterior MTL correlation with subsequent memory performance parallels data showing that pre-stimulus activity in the hippocampus prior to memory encoding predicts performance (Park & Rugg 2010), and that ongoing entorhinal/anterior hippocampal activity modulates memory performance (Fernández et al. 1999a; Olsen et al. 2009). Additionally, subsequent memory performance correlations with another default network hub, the retrosplenial cortex, was observed and might reflect pre-learning connectivity with other areas of the medial temporal lobe (Buckner et al. 2008). I cannot claim that any performance related brain activity during the ITI was pre-stimulus *per se*, only that as in previous work (Fernández et al. 1999; Peigneux et al. 2006) it continued during learning. Another possibility is that carryover activity from encoding periods aids memory encoding and thus subsequent memory performance, which has been previously observed in the MTL (Schon et al. 2004; Olsen et al. 2009; Ben-Yakov & Dudai 2011).

The persistence of hippocampal activity relative to task conditions throughout all offline phases complements previous work (Peigneux et al. 2006; Wig et al. 2008). These results also suggest an important role for the hippocampal formation in generating ongoing activity that is important for memory formation. Furthermore, these endogenous DMN correlations that predict memory performance (within 30 mins) around learning might reflect a role in early consolidation (Nadel et al. 2000; Wang & Morris 2010). This idea of rapid neocortical-hippocampal consolidation is supported by recent evidence showing rapid post-encoding synaptic tagging in task-relevant neocortical areas for hippocampal-dependent memories in rodents (Lesburguères et al, 2011).

Despite having too much noise in this sample for group-level inferences on participants in the 7T experiment, the technique still holds promise. The ability to investigate hippocampal subfields like CA1 and CA3 with high resolution and still image the rest of the brain is quite promising, but sufficient measures to avoid physiological artefacts in resting state (and task) scans is necessary (Birn et al. 2008; Fox et al. 2009; Murphy et al. 2009; Handwerker et al. 2012). With the rapid development of artefact removal and higher quality scan sequences, these issues should be remedied relatively soon.

Given the relatively low anatomical resolution of the 3T study, I cannot claim a high degree of anatomical specificity within the hippocampal formation and parahippocampus. However, future research will be able to make better use of the advanced spatial resolution and signal quality of UHF MR to investigate MTL substructure functional connectivity with the whole brain during offline periods. My results suggest a possible consolidation-related shift within human MTL substructures from performance predictive connectivity between MTL structures

prior to learning and between the MTL and neocortex after learning that may parallel previous findings in the cortex (Nadel et al. 2000; Takashima et al. 2006; Takashima et al, 2009; Tambini et al. 2010; van Kesteren et al. 2010). Another promising direction is to correlate the integrity of connectivity within the default network with behaviour, which may allow for systemic monitoring of its contribution to memory storage.

7.5 **Conclusions**

My preliminary results suggest that hippocampal activity at all time points before, during, and after learning is important in determining subsequent memory performance, but that hippocampal performance-related connectivity dynamically shifts to task-relevant regions after encoding. My results suggest a behavioural relevance for the default network in learning, although more definitive data needs to be collected to substantiate my claims.

Chapter 8

General Discussion

8.1 Overview

The overarching goal of my thesis was to investigate the relationship between animal and human models of hippocampal function in spatial memory. I used interactive spatial navigation paradigms, similar to those used in rodents, while participants were measured with neuroimaging techniques such as fMRI and MEG. I uncovered that the human hippocampus coordinates self-directed learning through the exploratory movement driven theta rhythm (Chp. 4) and also determined that mPFC interregional and cross-frequency coupling helps coordinate spatial memory retrieval on the same task (Chp. 5). I then investigated the effect environmental and object novelty had on a similar task using fMRI and found that the amygdala initially encoded object novelty during learning, while the hippocampus encoded environmental novelty (Chp. 6). Lastly, 3T and 7T fMRI combined resting state/spatial navigation experiments were conducted to investigate spatial memory formation (Chp.7) and preliminary evidence suggests that default mode network fluctuations in connectivity, including the hippocampus, might reflect prior spatial learning.

In the final chapter of my thesis, I explore the role of hippocampal theta oscillations on cognition and consider how my fMRI and MEG results might further advance our knowledge. I then discuss the potential significance of interregional and cross-frequency coupling for memory. Afterwards, I focus on the role other structures such as the basal forebrain/amygdala (along with the hippocampal formation) might hold in learning new objects and environments. Finally, I close by discussing the potential behavioural relevance of the default mode network and how oscillatory activity forms a common thread in my experimental findings.

8.2 Theta and cognition

A key advantage of measuring neural oscillations is that researchers can measure data in different model systems ranging from freely behaving rodents to humans participants performing complex cognitive tasks. Yet until recently, finding hippocampal theta oscillations in humans has proven elusive. Other than a few studies in non-human primates (Watanabe & Niki 1985; Stewart & Fox 1991; Rolls et al. 1997; Georges-Francois et al. 1999; Hori et al. 2003, 2005) and intracranial recordings in humans (Halgren et al. 1978; Arnolds et al. 1980) with unclear behavioural correlates, there was very little evidence relating the exploratory type I hippocampal theta rhythm measured in the rodent to any electrophysiological activity elicited by human mnemonic function. The introduction of virtual reality navigation tasks for epileptic patients with implanted hippocampal depth electrodes has given researchers the ability to use similar spatial memory tasks as ones used with rodents and investigate the same correlates in the human hippocampus (Burgess et al. 2002). Similar to rodents, in Chp. 4 I found that movement-related theta is highest in amplitude at movement initiation and accompanied by a reduction in theta power (not frequency like in rodents) in novel environments. Type I dominated theta is often thought to serve as memory encoding state in freely behaving rats when there is no explicit memory task and in Chp. 4, I demonstrated how this capability could occur by showing that the human equivalent of type I theta supports memory encoding by coordinating exploratory movements in the service of self-directed learning (Kaplan et al. 2012).

An emerging literature of MEG and iEEG studies has demonstrated correlations between theta power in the hippocampus/medial temporal lobe and memory performance (Cornwell et al. 2008; Guderian et al. 2009; Fell et al. 2011;

Poch et al. 2011; Lega et al. 2012; Guitart-Masip et al. 2013). Furthermore, recent findings have implicated the importance of single unit phase-locking to the hippocampal theta rhythm (Rutishauser et al. 2010). Rutishauser and colleagues (2010) found the precision of phase locking of amygdala and hippocampal neurons to the LFP theta rhythm during memory encoding predicted whether an encoded item would be successfully remembered. This finding indicates that hippocampal phase concentration could serve as a diagnostic of system state. In addition to hippocampal theta, a distinct theta rhythm has been reported in the human entorhinal cortex (Mormann et al. 2008) and preliminary evidence suggests that direct stimulation of entorhinal cortex resets hippocampal theta and improves performance on a spatial memory task (Suthana et al. 2012).

8.3 Human and animal theta differences across species

In the freely moving rat, theta is the dominant oscillation in the hippocampus (Vanderwolf 1969), and amplitudes of one millivolt are not unusual. By contrast, finding hippocampal theta oscillations in humans has proven elusive until recently. Other than a relatively small number of intracranial EEG recordings in humans (Halgren et al. 1978; Arnolds et al. 1980) with unclear behavioural correlates, there was very little evidence relating the hippocampal theta rhythm measured in the rodent to electrophysiological activity elicited by human mnemonic function. Furthermore, human and monkey hippocampal theta oscillations (4-8 Hz) appear to be much more transient in duration than the rodent hippocampal theta rhythm measured during exploration (Jacobs & Kahana 2010). This is only further confounded by differences in frequency, where often the LFP is not dominated by the centre of the theta band like with rodents, but by either lower 1-4 Hz delta

frequencies or higher frequencies in the 8-12 Hz alpha band (Jacobs & Kahana 2010; Lega et al. 2012).

One problem for across-species comparisons is that the historical scalp-EEG derived frequency boundaries used in human research are somewhat arbitrary, and the frequency of characteristic oscillations (e.g. eyes-closed alpha) may vary considerably even in aged-matched subjects, such that *a priori* fixed-band analyses may mask real effects (Klimesch 1999). A key challenge for reconciling animal-human data is that theta-behaviour links have mostly been characterised in freely-moving rodents, while there are few recordings in non-human primates (Rolls et al. 1997; Georges-Francois et al. 1999; Hori et al. 2003, 2005) and no recordings exist of theta during human locomotion, where virtual reality video games are more commonly used. One feasible possibility for species-matching is to record theta from ambulating mammals including humans in virtual reality setups where the subject's ambulation updates the visual scene (Harvey et al. 2009; Chen et al. 2013). Further evidence of the utility of VR systems for measuring theta comes from targeted electrode recordings in rodents showing the presence of movement-related hippocampal theta during ambulation in a virtual reality system, even when experiencing virtual visual motion without physically moving (Chen et al. 2013).

Still, it is uncertain whether human hippocampal delta oscillations during virtual exploration (Ekstrom et al. 2005; Watrous et al. 2011) are more analogous to theta in rodents, or whether the 8 Hz amplitude increases seen during some components of goal-directed virtual navigation (Ekstrom et al. 2005; Exp. 1) and purely mnemonic tasks (Fell et al. 2011; Lega et al. 2012) are more relatable to rodent theta, see Watrous et al. in press. Notably some ~8 Hz oscillatory activity extends well into the 8-12 Hz alpha band (Fell et al., 2011; Lega et al. 2012), which

is interesting given hypotheses that posit that alpha inhibition in the neocortex renders stored neural representations more sparse during memory formation (Axmacher et al. 2006). Further, the proposed cognitive mechanism of transient hippocampal theta triggering top-down alpha inhibition from the neocortex may relate to early ideas on the hippocampal theta rhythm and behavioural inhibition (Douglas 1969). How these ideas match previous ideas on theta and cross-frequency coupling is unclear and it will take further research to unlock how hippocampal oscillations might guide mnemonic function.

Similar to across species differences in theta, discrepancies related to shorter duration and lower frequencies have been observed when investigating the human/non-human primate homologs of fast gamma (>100 Hz) and sharp-wave ripple activity. 80-150 Hz ripple activity typically lasting around 50 ms has been observed in both humans (Axmacher et al. 2008) and non-human primates (Skaggs et al. 1997; Logothetis et al. 2012), which is much lower than the traditional ~200 Hz activity in rodent recordings. Despite these differences, Axmacher and colleagues (2008) found that increased ripple events during a short nap after a memory encoding task predicted successful post-nap memory recall, which matched later findings in rodents also showing behavioural relevance for ripples (for examples later shown in rodents see Girardeau et al. 2009; Ramadan et al. 2009; Jadhav et al. 2012). Furthermore, robust >200 Hz hippocampal activity has also been observed, however it appears to directly relate to epilepsy pathology (Bragin et al. 1999; for review see Engel Jr et al. 2009). Other non-pathological >100 Hz fast gamma activity in the parahippocampal gyrus was found during slow-wave sleep, but hippocampal gamma was mostly below 100 Hz (Le Van Quyen et al. 2010).

8.4 Frontal midline theta and cognition

In humans, frontal midline theta is often viewed as a surrogate to the hippocampal theta usually observed in rodent recordings (Mitchell et al. 2008) and numerous studies have related human frontal midline theta oscillations to memory performance (see Klimesch 2001; Addante et al. 2011 for examples). However with advances in intracranial recordings and non-invasive MEG source reconstruction, investigations into the theta rhythm of the human hippocampus and medial temporal lobe are becoming more prevalent. Using these advances in Chapter 5, I found that indeed the mPFC theta rhythm works in tandem with MTL theta during cued memory retrieval through phase-locking between oscillatory sources in both regions. These findings fit emerging evidence implicating the importance of frontal midline theta and the human mPFC in memory formation and recall (Anderson et al. 2010; Watrous et al. 2013). However, the exact role that this region and its rhythm may hold is unclear. Judging by the results of Chapter 5, it is becoming increasing clear that interregional coupling between commonly observed rhythms such as frontal midline theta and neocortical gamma might underlie many cognitive processes. Still, it is debatable whether it is even necessary to perform species matching between rodent and primate model systems of hippocampus-mPFC interactions, especially given the cross-species differences in frontal midline (Gaffan 2002).

8.5 The role of cross-frequency and interregional coupling in memory

In Experiment 2, the appearance of the retrieval cue (i.e. to-be-remembered object) elicited fast (65-85 Hz) neocortical gamma oscillations and I found that the amplitude of these gamma oscillations was locked to the phase of the mPFC theta

rhythm. Furthermore, the consistency of this phase-amplitude coupling predicted subsequent memory performance during actual memory retrieval of object locations. These findings add further evidence to the importance of cross-frequency and interregional coupling and I will now detail how these phenomena might underlie cognitive processes.

The utility of oscillations might come from their ability to temporally organize processing within a region and also support effective inter-regional communication. Therefore, if processing is temporally organised into chunks, but dispersed across two brain regions, then coherent temporal organisation is needed across those regions. For example, if communication is organised such that information concerning different objects occurs in different cycles of gamma, and this information is spread across multiple brain regions, then that local gamma rhythms must be coherent for the correct object-bindings to be maintained. Equally, if neural activity in two regions each tend to oscillate (e.g. due to local feedback inhibition), coupling the activity in both regions via inter-regional synaptic transmission will tend to lead to coherence in the local oscillations. This view, of oscillatory coherence as a diagnostic of functional inter-regional coupling, is elaborated in the "communication through coherence" hypothesis (Fries, 2005).

Another form of interregional oscillatory coupling comes from investigation of low frequency (0.01-0.1 Hz) endogenous fluctuations in the blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) signal in humans. One of the primary endogenous brain networks, commonly referred to as the 'default mode network', centres on the hippocampus, parietal midline and mPFC (Raichle et al. 2001; Buckner et al. 2008) and shows anatomical overlap with fMRI spatial activity patterns observed during spatial and autobiographical memory tasks

(Hassabis & Maguire 2007; Buckner & Carroll 2007). In parallel research with MEG, a study by Hipp et al. (2012) observed ongoing (5-7 Hz) theta synchronicity between the human MTL and other default mode network regions. Related to both electrophysiological and fMRI signals, Logothetis et al. (2012) used hippocampal electrode recordings simultaneously with fMRI to measure hippocampal ripple events in both awake and sleeping primates. The authors found that ripple events were phase-locked to the hippocampal delta rhythm and inhibited endogenous BOLD activity in neocortical areas like the default mode network, but increased activity in subcortical brain regions.

Additionally, there is now an emerging literature investigating inter-areal coupling in humans using ECoG recordings (Watrous et al. 2013) and non-invasive MEG source connectivity techniques (Lever et al. in press) to explore phase interactions that could underlie mnemonic function. Interregional and cross-frequency coupling does not appear to be behaviourally specific and has been observed during spatial memory, evaluative and anxiety-related behaviours in health and disease (for review see Lever et al. in press).

A potential mechanism for organizing distributed representations, particularly relevant in mnemonic function, is cross-frequency coupling. In the context of memory tasks, cross-frequency coupling usually entails the phase of a low-frequency oscillation, like the hippocampal theta rhythm, locking (i.e., showing coherence) with either the phase or amplitude/power of a higher frequency oscillation, like gamma. These phase-phase and phase-amplitude (observed in Exp. 2) couplings could work in the service of memory formation and retrieval by providing a mechanism to organize learned sequences (Jensen & Colgin, 2007).

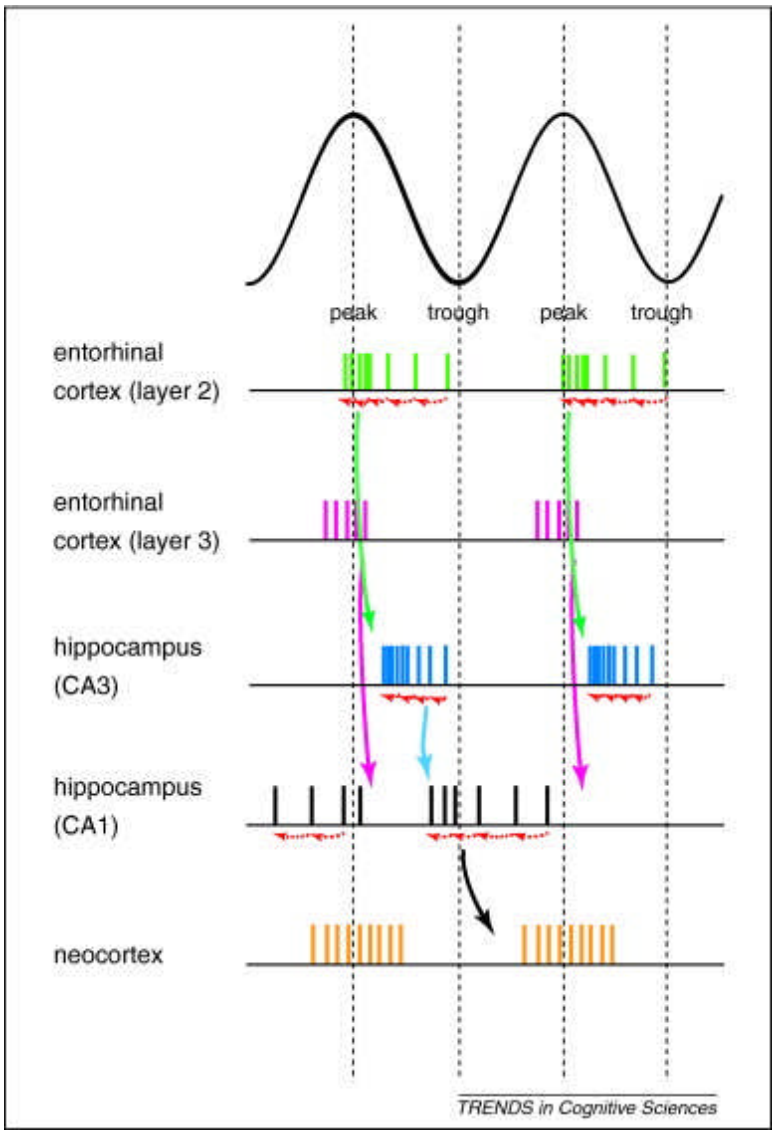

Figure 27: The hippocampus as a signal integration hub
Diagram taken from Battaglia et al. 2011 *Trends Cog Sci* showing the relationship between the hippocampal theta rhythm and rhythms in the entorhinal cortex and neocortex in the freely behaving rodent. Note phase precession (red arrows) in CA1 and CA3 of the hippocampus and hippocampal theta phase-locking to neocortical neural firing, thus showing the integrative capability of the hippocampal theta rhythm. Based on Mizuseki et al. 2009, during each place field traversal, the hippocampal firing phase moves from a phase compatible with the entorhinal input structure phase, to a phase where entorhinal inputs are minimal. Therefore, most firing can arise from intrinsic dynamic processing of previous inputs that occurred much earlier.

8.6 Why is the hippocampus involved in movement?

After detailing the cognitive implications of the type I theta rhythm, it is interesting to note from experiment 1 that virtual movement initiation versus stationary periods during spatial learning activated the hippocampus, while stationary periods activated the parahippocampal cortex. This finding strengthens the argument that the movement-related theta rhythm helps aid the learning of sequences during encoding because hippocampal fMRI activations during movement also correlated with increased subsequent memory performance. This idea appears to fit well with the idea of the human (and possibly rodent) hippocampus being crucial for active versus passive learning (Voss et al. 2011). Additionally, past studies in rodents who either volitionally moved or were passively moved in a motorised cart (Kim et al. 2005; Terrazas et al. 2005) showed decreased theta during passive movement. A similar reduction in theta power is seen when rodents passively watch a virtual environment moving past them compared to driving the movement of the environment by running on a trackball (Chen et al. 2013). The fact that hippocampal activity and the theta rhythm correlate more strongly with performance during movement initiation in Experiment 1, is at least vaguely consistent with this idea. It will be important to investigate if there is any specific role for exploratory movements within volitional learning to begin to interpret these results more fully, see for example (Gureckis et al. 2012).

8.7 Amygdala and non-emotional learning

The majority of studies investigating amygdala function in humans and other species have focused on fear conditioning and, to some degree, reinforcement learning and value-guided choice (Phelps 2005; Adolphs 2010; Morrison & Salzman

2010). This has resulted in researchers viewing the amygdala as being predominantly involved in affective or evaluative processing. However, this view has largely ignored the non-emotional role of the amygdala in perception and memory. There is a well documented literature implicating the amygdala in surprise detection (Halgren et al. 1978), arousal (Thoresen et al. 2011), and vividness (Kensinger et al. 2011). Furthermore, there is growing evidence that the amygdala plays a key role in familiarity judgments in recognition memory (Farovik et al. 2010). Taken together, this work seems to implicate a role for the amygdala in novelty detection. The findings presented in Experiment 3 could support this view by showing that the amygdala initially encodes object novelty during active learning, but then rapidly shows the opposite effect as an object becomes more familiar and shows more rapid temporal attenuation than the hippocampal response to environmental novelty. The idea that the amygdala is important for novelty detection makes sense when considering that social and affective cues must be rapidly detected and usually make up sub-components of a larger context (i.e. 'facial expression on a face' 'sudden movement in an environment"), while the hippocampus might serve the same function, but in a contextual sense (i.e. 'gradual changes in environment' and 'threatening anxiety-like states') which would take longer because more details and viewpoints would need to be integrated into a cohesive representation.

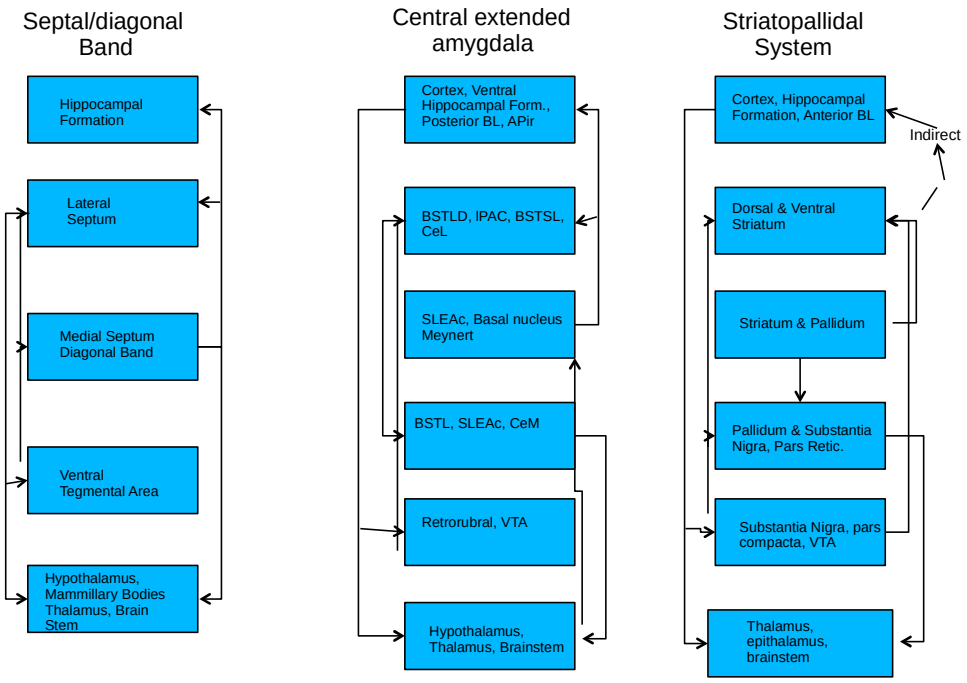

Figure 28: Basal forebrain projections
Adapted from Alheid 2003 Annals of NY Acad Science showing the different projection from the basal forebrain through the septal/diagonal band (theta generating circuit), central extended amygdala, and striatopallidal system. Note BSTL stands for bed nucleus of the stria terminalis, SLEAc is extended amygdala, CeM is central nucleus of the amygdala, VTA is ventral tegmental area, BL is basolateral amygdala, and lPAC is lobus paracentralis.

The role of the amygdala in learning and detecting novelty adds to an emerging literature of associative learning, mismatch detection and recognition memoy in other areas of the medial temporal lobe such as the hippocampus (Knight 1996; Strange et al. 2005; Kumaran et al. 2006), parahippocampal cortex (Preston et al. 2010; Howard et al. 2012) and perirhinal cortex (Duzel et al. 2003; Aggleton & Brown 2001; Murray et al. 2007). Research is still in the nascent stages of disambiguating how these different structures function in novelty processing. There have been attempts to link the hippocampus to probability (for an example see Schapiro et al. 2012) and detection of surprising stimuli (for an example see Strange

et al. 2005), mainly in the anterior hippocampus. Furthermore, much of the novelty detection capability we link to the amygdala in Experiment 3, i.e. detection and learning of novel items, was previously believed to be supported by the perirhinal cortex (PrC) (Aggleton & Brown 2001; Murray et al. 2003; Duzel et al. 2003; Ranganath & Ritchey 2012). However, evidence from the animal literature suggests that PrC is more important for determining novel relationships between multiple novel stimuli (Moses et al. 2002, 2005), while the relative novelty of an individual object could be encoded by the amygdala.

One potential reason why the amygdala might have been overlooked in favour of the perirhinal cortex, in terms of processing object novelty, is that the component of active learning in Experiment 3 is often not present in traditional stimulus-based familiarity judgments. Interacting with objects in a way that is appropriate to their broader behavioural context may increase amygdala activation (see King et al. 2006). An interesting potential avenue of study, possibly resolved will human iEEG (or single-neuron) recordings will be to disambiguate the contributions of novelty detection in anterior hippocampus, amygdala, and PrC. With new high-resolution image techniques (potentially helped with advances with 7T) that can measure functional activity in subregions of the amygdala, further distinctions can be made (Bach et al. 2011). Depending on the subregion, it might be possible to test whether the same cholinergic inputs that modify the hippocampal theta rhythm might affect amygdala/basal forebrain encoding of object novelty (see figure adapted from Alheid 2003). Furthermore, with recent links between hippocampal and amygdala theta synchrony (Seidenbecher et al. 2003) and previous work on the theta rhythm's modulation by environmental novelty, An interplay between different types of novelty and their effect on MTL theta could unlock many

insights into the cholinergic system and surprise (Yu & Dayan 2005; Hasselmo 2005). In sum, there may be a new picture emerging about the role that the amygdala plays in the initial stages of learning, and further research will be needed to isolate the exact contributions and time scales this learning entails.

8.8 Core MTL network & default mode network

Endogenous neural fluctuations (also known as 'resting-state' fluctuations) affect how upcoming information will be processed, but nobody knows exactly how or why this happens (Raichle et al. 2001; Buckner et al. 2008). One hypothesis posits that endogenous brain networks dynamically encode repertoires for future behaviour (Deco & Corbetta 2011). In experiment 4, I studied a prominent endogenous network, the default mode network (DMN), which anatomically overlaps with networks critical for spatial memory and fictive planning (Buckner & Carroll 2007; Hassabis & Maguire 2007). There is growing evidence that endogenous brain activity/fluctuations predict subsequent behaviour across different species (Arieli et al. 1996; Super et al. 2003; Fiser et al. 2004; Luczak et al. 2007; Luczak et al. 2009; Fiser et al. 2010; Sadaghiani et al. 2010; Luczak & Maclean 2012) and neural firing during spatial exploration (Dragoi & Tonegawa 2011) but the cognitive ramifications of this endogenous DMN activity are unknown (Raichle et al. 2001; Buckner et al. 2008). Findings in humans have demonstrated learning-induced (within-subject) endogenous changes (Lewis et al. 2009; Albert et al. 2009) and trait (between-subjects) characteristics of endogenous fluctuations that predict subsequent behaviour (Boly et al. 2007; Hesselmann et al. 2008a,b), particularly in the hippocampus (Wig et al. 2008; Wang et al. 2010). Furthermore, endogenous activity immediately prior to encoding of individual memories has also been found

to predict successful memory recall (Guderian et al. 2009; Park & Rugg 2010; Rutishauser et al. 2010). In preliminary fMRI data from Experiment 4, I found that endogenous hippocampal connectivity with other DMN hubs before learning predicts subsequent spatial memory performance. Taken together, these studies begin to relate endogenous fluctuations to behaviour and future work will determine the exact role endogenous DMN activity plays in memory formation

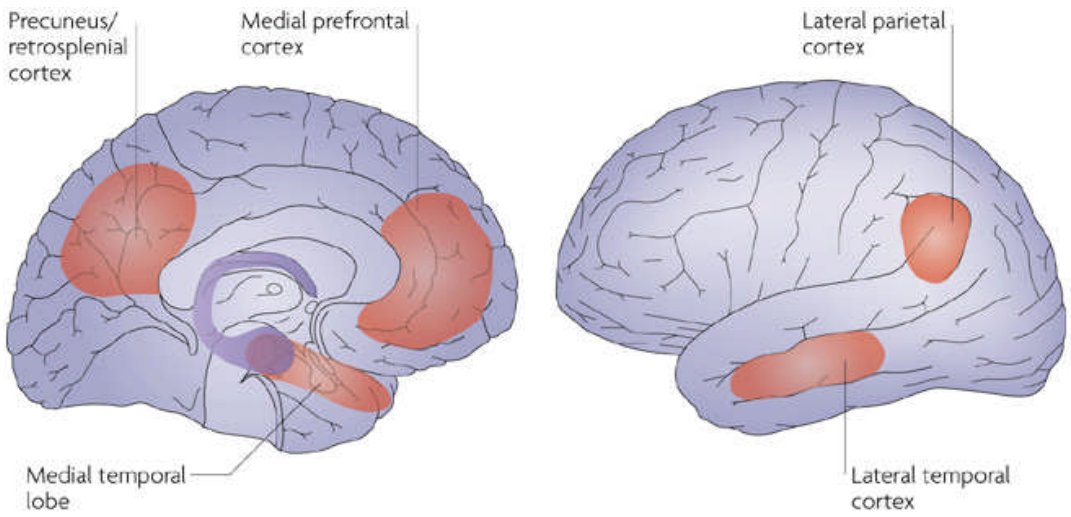

Figure 29: Anatomy of the default mode network
Taken from Schacter et al. 2007 *Nat Reviews Neuro* showing an anatomical schematic of the default mode network, which anatomically overlaps with regions that are crucial autobiographical, episodic, and spatial memory.

8.8.1 *What does it mean?*

There are many theories about why task-free or endogenous fluctuations in brain activity might relate to behaviour. Additionally, there is a growing body of literature demonstrating the importance of endogenous neuronal dynamics in cognition across different species, and data from rodent hippocampal preplay, replay and wheel-running showing that endogenously driven neuronal dynamics can predict novel spatial behaviour (Skaggs et al. 1996; Pastalkova et al. 2008; Dragoi & Tonegawa 2011). These findings have led to the compelling hypotheses that

endogenous neural dynamics reflect encoding of prior behaviour and neural preparation for future behaviour (Corbetta & Deco 2011). Thinking in terms of how this could be applied to the hippocampus, we can think of synchronized endogenous fluctuations in activity in the hippocampus and other memory-related structures like the mPFC as a dynamic exploration of previously learned sequences, in which the fluctuations between regions could reflect how these brain areas might prepare for the encoding of novel sequences (Sadaghiani et al. 2012). Preliminary evidence exists for this hypothesis in the rodent hippocampal theta rhythm (Dragoi & Tonegawa 2012), but further research on how this might correspond to interregional synchrony and changes in the BOLD signal is necessary.

8.9 Conclusion

The experiments in my thesis are a demonstration of how active spatial learning paradigms can extend findings from rodent studies of spatial cognition to human learning and memory. Through the use of interactive virtual reality spatial memory paradigms, I found evidence of virtual movement related theta power and hippocampal BOLD signal increases, which suggests that exploration related hippocampal activity occurs both in rodent and human spatial cognition and could underlie active learning in both species. Additionally, I found environmental novelty related theta power increases and hippocampal BOLD signal increases, implying that the hippocampus and the theta rhythm serve as contextual, but not generalised novelty detectors. Lastly, I found that hippocampal theta power prior to memory retrieval predicted subsequent memory retrieval performance, while hippocampal BOLD activity during encoding predicted subsequent memory performance. These mnemonic performance findings further highlight the importance of the

hippocampus in spatial memory formation. Taken together, these findings highlight the potential mnemonic relevance of findings from rodent spatial exploration experiments and serve as further demonstration that spatial paradigms could reveal the mechanisms supporting the role of the hippocampus in memory.

References

Abrahams S, Pickering A, Polkey CE, Morris RG (1997) Spatial memory deficits in patients with unilateral damage to the right hippocampal formation. Neuropsychologia 35: 11–24.

Addante RJ, Watrous AJ, Yonelinas AP, Ekstrom AD, Ranganath C (2011) Prestimulus theta activity predicts correct source memory retrieval. Proc Natl Acad Sci USA 108:10702-7.

Adhikari A, Topiwala MA, Gordon JA (2010) Synchronized activity between the ventral hippocampus and the medial prefrontal cortex during anxiety. Neuron 65: 257–269.

Adhikari A, Topiwala MA, Gordon JA (2011) Single units in the medial prefrontal cortex with anxiety-related firing patterns are preferentially influenced by ventral hippocampal activity. Neuron 71(5):898-910

Adolphs R (2010) What does the amygdala contribute to social cognition? Ann NY Acad Sci, 1191:42-61.

Albert NB, Robertson EM, Miall RC (2009) The resting human brain and motor learning. Curr Biology 19:1023-7.

Alheid GF (2003) Extended amygdala and basal forebrain. Ann NY Acad Sci 985:185-205

Andersson JL, Hutton C, Ashburner J, Turner R, Friston K (2001) Modeling geometric deformations in EPI time series. Neuroimage 13:903-919.

Arieli A, Sterkin A, Grinvald A, Aertsen A. (1996). Dynamics of ongoing activity: explanation of the large variability evoked cortical responses. Science 273:1868–71.

Arnolds DE, Lopes da Silva FH, Aitink JW, Kamp A, Boeijinga P (1980) The spectral properties of hippocampal EEG related to behaviour in man. Electroencephalograph Clin Neurophysiol 50:324:28

Asada H, Fukuda Y, Tsunoda S, Yamaguchi M, Tonoike M (1999) Frontal midline theta rhythms reflect alternative activation of prefrontal cortex and anterior cingulate cortex in humans. Neurosci Lett 274:4-14.

Ashburner J, Friston KJ (2005) Unified segmentation. Neuroimage 26:839-51.

Axmacher N, Mormann F, Fernández G, Elger CE, Fell J (2006) Memory formation by neuronal synchronization. Brain Res Rev 52:170-82.

Axmacher N, Elger CE, Fell J (2008) Ripples in the medial temporal lobe are relevant for human memory consolidation. Brain 131:1806-17.

Axmacher N, Cohen MX, Fell J, Haupt S, Dümpelmann M, Elger CE, Schlaepfer TE, Lenartz D, Sturm V, Ranganath C (2010a) Intracranial EEG correlates of expectancy and memory formation in the human hippocampus and nucleus accumbens. Neuron 65:541-9.

Axmacher N, Henseler M, Jensen O, Weinreich I, Elger C, Fell J (2010b) Cross-frequency coupling supports multi-item working memory in the human hippocampus. Proc Nat Acad Sci USA 107:3228-33.

Babiloni C, Vecchio F, Mirabella G, Buttiglione M, Sebastiano F, Picardi A, Di Gennaro G, Quarato PP, Grammaldo LG, Buffo P, Esposito V, Manfredi M, Cantore G, Eusebi F (2009) Hippocampal, amygdala, and neocortical synchronization of theta rhythms is related to an immediate recall during rey auditory verbal learning test. Hum Brain Mapp 30, 2077-89

Bach DR, Behrens TE, Garrido L, Weiskopf N, Dolan RJ (2011) Deep and superficial amygdala nuclei projections revealed in vivo by probabilistic tractography. J Neurosci 31:618-23.

Bagshaw MH, Mackworth NH, Pribram KH (1972) The effect of resections of the inferotemporal cortex or the amygdala on visual orienting and habituation. Neuropsychologia 10:153-62

Balderston NL, Schultz DH, Helmstetter FJ (2011) The human amygdala plays a stimulus specific role in the detection of novelty. Neuroimage, 55:1889-98.

Bandettini PA, Wong EC, Hinks RS, Tikofsky RS, Hyde JS (1992) Time course EPI of human brain function during task activation. Magn Reson Med 25:390-7

Bandettini PA (2009) What's new in neuroimaging methods? Ann NY Acad Sci 1156:260-93.

Bandettini PA, Bowtell R, Jezzard P, Turner R (2012) Ultra high field systems and applications at 7T and beyond: progress, pitfalls, and potential. Magnetic Res Med 67:317-321.

Bar M, Aminoff E (2003). Cortical analysis of visual context. Neuron 38:347–358.

Barnes GR, Hillebrand A (2003) Statistical flattening of MEG beamformer images. Hum Brain Mapp 18:1-12.

Bast, T, Wilson IA, Witter MP, and Morris RG (2009) From rapid place learning to behavioral performance: a key role for the intermediate hippocampus. PLoS Biol, 7:e1000089.

Battaglia FP, Benechenane K, Sirota A, Pennartz CM, Wiener SI (2011) The hippocampus: hub of brain network communication for memory. Trends Cogn Sci 7:310-8.

Beckmann CF, DeLuca M, Devlin JT, Smith SM (2005) Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci 360:1001-13.

Belliveau JW, Kennedy DN Jr, McKinstry RC, Buchbinder BR, Weisskoff RM, Cohen MS, Vevea JM, Brady TJ, Rosen BR (1991) Functional mapping of the human visual cortex by magnetic resonance imaging. Science 254:716-9

Belluscio MA, Mizuseki K, Schmidt R, Kempter R, G Buzsaki (2012) Cross-Frequency Phase–Phase Coupling between Theta and Gamma Oscillations in the Hippocampus, Journal of Neuroscience, 32:423-435

Benchenane K, Peyrache A, Khamassi M, Tierney PL, Gioanni Y, Battaglia FP, Wiener SI (2010) Coherent theta oscillations and reorganization of spike timing in the hippocampal- prefrontal network upon learning. Neuron 66:921-36.

Ben-Yakov A, Dudai Y (2011) Constructing realistic engrams: poststimulus activity of hippocampus and dorsal striatum predicts subsequent episodic memory. J Neurosci 31:9032-42.

Berens P (2009) CircStat: A Matlab toolbox for circular statistics. J Statistical Software 31(10):i10

Berke J. D, Okatan M, Skurski J, Eichenbaum H. B (2004) Oscillatory entrainment of striatal neurons in freely moving rats. Neuron 43: 883–896.

Bird CM, Burgess N (2008) The hippocampus and memory: insights from spatial processing. Nat Rev Neurosci 9:182-94.

Bird, CM, Capponi, C., King, JA, Doeller, CF, Burgess, N (2010) Establishing the boundaries: the hippocampal contribution to imagining scenes. J. Neuroscience 30: 11688–11695.

Birn RM, Murphy K, Bandettini PA (2008) The effect of respiration variations on independent component analysis results of resting state functional connectivity. Hum Brain Mapp 29:740-50.

Biswal B, Yetkin FZ, Haughton VM, Hyde JS (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 34:537-41.

Blackford JU, Buckholtz JW, Avery SN, Zald DH (2010) A unique role for the human amygdala in novelty detection. Neuroimage 50:1188-93.

Bland BH, Oddie SD (2001) Theta band oscillation and synchrony in the hippocampal formation and associated structures: the case for its role in sensorimotor integration. Behav Brain Res 127:119-36.

Bohbot V, Kalina M, Stepankova K, Spackova N, Petrides M, Nadel L (1998) Spatial memory deficits in patients with lesions to the right hippocampus and to the right parahippocampal cortex. Neuropsychologia 36: 1217–1238.

Boly M, Balteau E, Schnakers C, Degueldre C, Moonen G, Luxen A, Phillips C, Peigneux P, Maquet P, Laureys S (2007) Baseline brain activity fluctuations predict somatosensory perception in humans. Proc Natl Acad Sci USA, 104:12187-92.

Bostock H, Muller RU, Kubie JL (1991) Experience-dependent modifications of hippocampal place cell firing. Hippocampus, 1:193-205.

Bragin A, Engel J Jr, Wilson CL, Fried I, Buzsaki G (1999) High-frequency oscillations in human brain. Hippocampus 9(2):137-42.

Brandon MP, Bogaard AR, Libby CP, Connerney MA, Gupta K, Hasselmo ME (2011) Reduction of theta rhythm dissociates grid cell spatial periodicity from directional tuning. Science 332(6029):595-9

Brett M, Anton JL, Valabregue R, Poline JB (2002) Region of interest analysis using an SPM toolbox. OHBM Sendai.

Brookes MJ, Woolrich M, Luckhoo H, Price D, Hale JR, Stephenson MC, Barnes GR, Smith SM, Morris PG (2011) Investigating the electrophysiological basis of resting state networks using magnetoencephalography. Proc Natl Acad Sci USA 108:16783-8.

Brown MW, Aggleton JP (2001) Recognition memory: what are the roles of the perirhinal cortex and hippocampus? Nat Rev Neurosci, 2:51-61.

Brown TI, Ross RS, Keller JB, Hasselmo ME, Stern CE (2010) Which way was I going? Contextual retrieval supports the disambiguation of well learned overlapping navigational routes. J Neurosci, 21:7414–7422.

Brown TI, Ross RS, Tobyne SM, Stern CE (2012) Cooperative interactions between hippocampal and striatal systems support flexible navigation. Neuroimage, 60:1316-30.

Brown TI, Stern CE (2013) Contributions of medial temporal lobe and striatal memory systems to learning and retrieving overlapping spatial memories. Cereb Cortex, Advanced Online Publication

Buckley MJ, Gaffan D (1998) Perirhinal cortex ablation impairs configural learning and paired-associate learning equally. Neuropsychologia, 36:535-46.

Buckner RL, Bandettini PA, O'Craven KM, Savoy RL, Petersen SE, Raichle ME, Rosen BR (1996) Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. Proc Natl Acad Sci USA, 93:14878-83.

Buckner RL, Carroll DC (2007) Self-projection and the brain. Trends Cogn Sci, 11:49-57.

Buckner RL, Andrews-Hanna JR, Schacter DL (2008) The brain's default system: anatomy, function, and relevance to disease. Ann NY Acad Sci, 1124:1-38.

Buckner RL (2010) The role of the hippocampus in prediction and imagination. Annu Rev Psychol, 61:27-48.

Bullmore E, Sporns O (2009) Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci, 10:186-98

Burgess N, Becker S, King JA, O'Keefe J (2001) Memory for events and their spatial context: models and experiments. Phil. Trans. R. Soc. Lond. B, 356:1493–1503

Burgess N, Maguire E. A, O'Keefe J (2002) The human hippocampus and spatial and episodic memory. Neuron, 35: 625–641

Burgess N (2008) Spatial cognition and the brain. Ann NY Acad Sci, 1124:77-97

Bussey TJ, Muir JL, Aggleton JP (1999) Functionally dissociating aspects of event memory: the effects of combined perirhinal and postrhinal cortex lesions on object and place memory in the rat. J Neurosci, 19:495-502.

Bragin A, Jando G, Nadasdy Z, Hetke J, Wise K, Buzsaki G (1995) Gamma (40-100 Hz) oscillation in the hippocampus of the behaving rat. J Neurosci 15:47-60.

Buzsaki G (2002) Theta oscillations in the hippocampus. Neuron 33:325–340.

Buzsaki G. (2006) Rhythms of the brain. New York: Oxford University Press.

Buzsaki G, Wang XJ (2012) Mechanisms of gamma oscillations. Annu Rev Neurosci 35:203-25.

Buzsaki G, Moser EI (2013) Memory, navigation and theta rhythm in the hippocampal-entorhinal system. Nat Neurosci 16:130-8.

Byrne P, Becker S, Burgess N (2007) Remembering the past and imagining the future: a neural model of spatial memory and imagery. Psychol Rev 114:340-75.

Canolty RT, Edwards E, Dalal SS, Soltani M, Nagarajan SS, Kirsch HE, Berger MS, Barbaro NM, Knight RT (2006) High gamma power is phase-locked to theta oscillations in human neocortex. Science 313:1626-8.

Canolty RT, Knight RT (2010) The functional role of cross-frequency coupling. Trends Cogn Sci 14:506-15.

Caplan JB, Madsen JR, Schulze-Bonhage A, Aschenbrenner-Scheibe R, Newman E. L, Kahana MJ (2003) Human theta oscillations related to sensorimotor integration and spatial learning. J Neurosci 23: 4726–4736.

Cashdollar N, Malecki U, Rugg-Gunn FJ, Duncan JS, Lavie N, Duzel E (2009) Hippocampus-dependent and -independent theta-networks of active maintenance. Proc Natl Acad Sci USA 106:20493-20498.

Chen G, King JA, Burgess N, O'Keefe J (2013) How vision and movement combine in the hippocampal place code. Proc Natl Acad Sci USA 110(1):378-83

Colgin LL, Denninger T, Fyhn M, Hafting T, Bonnevie T, Jensen O, Moser MB, Moser EI (2009) Frequency of gamma oscillations routes flow of information in the hippocampus. Nature 462:353-7.

Cornwell BR, Johnson LL, Holroyd T, Carver FW, Grillon C (2008) Human hippocampal and parahippocampal theta during goal-directed spatial navigation predicts performance on a virtual Morris water maze. J Neurosci 28: 5983–5990.

Cornwell BR, Salvadore G, Colon-Rosario V, Latov DR, Holroyd T, Carver FW, Coppola R, Manji HK, Zarate CA Jr, Grillon C (2010) Abnormal hippocampal functioning and impaired spatial navigation in depressed individuals: evidence from whole-head magnetoencephalography. Am J Psychiatry 167: 836–844.

Cornwell BR, Arkin N, Overstreet C, Carver FW, Grillon C (2012) Distinct contributions of human hippocampal theta to spatial cognition and anxiety. Hippocampus, 22:1848-59.

Cox, RW (1996) AFNI : software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res. 29:162-73.

Craik F. I. M (1986) A functional account of age differences in memory. In: Klix F, Hagendorf H, editors. Human memory and cognitive capabilities: mechanisms and performances. Holland: Elsevier. pp. 409–422.

Davachi L, Mitchell JP, Wagner AD (2003) Multiple routes to memory: distinct medial temporal lobe processes build item and source memory. Proc Natl Acad Sci U S A, 100:2157–2162

de Araujo DB, Baffa O, Wakai RT (2002) Theta oscillations and human navigation: a magnetoencephalography study. J Cogn Neuosci, 14:70–78

Deco G, Corbetta M (2011) The dynamical balance of the brain at rest. The Neuroscientist, 17:107-123

Deco G, Jirsa V, McIntosh AR (2011) Emerging concepts for the dynamical organization of resting-state activity in the brain. Nat Rev Neuro, 12:43-56.

Desgranges B, Baron JC, de la Sayette V, Petit-Taboue MC, Benali K, Landeau B, Lechevalier B, Eustache F (1998) The neural substrates of memory systems

impairment in Alzheimer's disease: A PET study of resting brain glucose utilization. Brain, 121:611-31.

Diekelmann S, Born J (2010) The memory function of sleep. Nat Rev Neurosci 11:114-26.

DeCouteau W. E, Thorn C, Gibson D. J, Courtemanche R, Mitra P, Kubota Y, Graybiel AM (2007) Learning related striatal and hippocampal theta rhythms during acquisition of a procedural maze task. Proc Natl Acad Sci U S A 104: 5644–5649.

Delorme A, Makeig S (2004) EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics. Journal of Neurosci Meth 134:9-21.

Diana RA, Yonelinas AP, Ranganath C (2007) Imaging recollection and familiarity in the medial temporal lobe: a three-component model. Trends Cogn Sci 11:379-86.

Doeller CF, King J, Burgess N (2008a) Parallel striatal and hippocampal systems for landmarks and boundaries in spatial memory. Proc Natl Acad Sci U S A 105: 5915–5920.

Doeller CF, Burgess N (2008b) Distinct error-correcting and incidental learning of location relative to landmarks and boundaries. Proc Natl Acad Sci U S A 105: 5909–5914.

Doeller C.F, Barry C, Burgess N (2010) Evidence for grid cells in a human memory network. Nature 463: 657–661.

Doeller CF, Kaplan R (2011) Parahippocampal cortex: translating vision into space. Curr Biol 21:589-91.

Dombeck DA, Khabbaz AN, Collman F, Adelman TL, Tank DW (2007 Imaging large-scale neural activity with cellular resolution in awake, mobile mice. Neuron, 56:43-57.

Domnisoru C, Kinkhabwala AA, Tank DW (2013) Membrane potential dynamics of grid cells. Nature, 495(7440):199-204

Douchamps V, Jeewajee A, Blundell P, Burgess N, Lever C (2013) Evidence for encoding versus retrieval scheduling in the hippocampus. J Neurosci, 33:8650-7

Douglas RJ (1969) Hippocampal theta and disinhibition: a counterreply. Psychol Rev, 24:583-586.

Dragoi G, Tonegawa S (2011) Preplay of future place cell sequences by hippocampal cellular assemblies. Nature 469:397–401

Duzel E, Penny WD, Burgess N (2010) Brain oscillations and memory. Curr Opin Neurobiol 20:143-9.

Eichenbaum H, Yonelinas AP, Ranganath C (2007) The medial temporal lobe and recognition. Annu Rev Neurosci, 30:123-52.

Ekstrom AD, Kahana MJ, Caplan JB, Fields TA, Isham EA, Newman EL, Fried I (2003) Cellular networks underlying human spatial navigation. Nature 425:184-8

Ekstrom AD, Caplan J. B, Ho E, Shattuck K, Fried I, Kahana MJ (2005) Human hippocampal theta activity during virtual navigation. Hippocampus 15: 881–889.

Ekstrom A, Suthana N, Millett D, Fried I, Bookheimer S (2009) Correlation between BOLD fMRI and theta-band local field potentials in the human hippocampal area. J Neurophysiol 101: 2668–2678.

Ekstrom A (2010) How and when the fMRI BOLD signal relates to underlying neural activity: the danger in dissociation. Brain Res Rev 62: 233–244.

Engel J Jr, Bragin A, Staba R, Mody I (2009) High-frequency oscillations: what is normal and what is not? Epilepsia 50:598-604.

Epstein RA, Kanwisher N (1998). A cortical representation of the local visual environment. Nature 392:598–601.

Epstein R, Harris A, Stanley D, Kanwisher N (1999) The parahippocampal place area: recognition, navigation, or encoding? Neuron, 23:115-25.

Epstein RA (2008) Parahippocampal and retrosplenial contributions to human spatial navigation. Trends Cog Sci 12:388-96.

Euston DR, Gruber AJ, McNaughton BL (2012) The role of medial prefrontal cortex in memory and decision making. Neuron 76:1057-70.

Ewbank MP, Schluppeck D, Andrews TJ (2005) fMR-adaptation reveals a distributed representation of inanimate objects and places in human visual cortex. Neuroimage, 28:268-79.

Farovik A, Place RJ, Miller DR, Eichenbaum H (2011) Amygdala lesions selectively impair familiarity in recognition. Nat Neurosci, 14:1416-7.

Fell J, Klaver P, Lehnertz K, Grunwald T, Schaller C, Elger CE, Fernández G (2001) Human memory formation is accompanied by rhinal-hippocampal coupling and decoupling. Nat Neurosci, 4:1259-64.

Fell J, Klaver P, Elfadil H, Schaller C, Elger CE, et al. (2003) Rhinal-hippocampal theta coherence during declarative memory formation: interaction with gamma synchronization? Eur J Neurosci, 17:1082–1088.

Fell J, Ludowig E, Rosburg T, Axmacher N, Elger CE (2008) Phase-locking within human mediotemporal lobe predicts memory formation. Neuroimage 43:410-9.

Fell J, Axmacher N (2011) The role of phase synchronization in memory processes. Nat Rev Neuro, 12:105-118.

Fell J, Ludowig E, Staresina BP, Wagner T, Kranz T, Elger CE, Axmacher N (2011) Medial temporal theta/alpha power enhancement precedes successful memory encoding: evidence based on intracranial EEG. J Neurosci, 31:5392-97.

Fernández G, Brewer JB, Zhao Z, Glover GH, Gabrieli JD (1999a) Level of sustained entorhinal activity at study correlates with subsequent cued-recall performance: a functional magnetic resonance imaging study with high acquisition rate. Hippocampus, 9:35-44.

Fernández G, Effern A, Grunwald T, Pezer N, Lehnertz K, Dumplemann M, Van Roost D, Elger CE (1999b) Real-time tracking of memory formation in the human rhinal cortex and hippocampus. Science, 285(5433):1582-5.

Fiser J, Chiu C, Weliky M (2004) Small modulation of ongoing cortical dynamics by sensory input during natural vision. Nature, 431:573-8.

Fiser J, Berkes P, Orban G, Lengyel M (2010) Statistically optimal perception and learning: from behavior to neural representations. Trends Cogn Sci, 14:119-30.

Fletcher PC, Shallice T, Frith CD, Frackowiak RS, Dolan RJ (1996) Brain activity during memory retrieval. The influence of imagery and semantic cueing. Brain, 119:1587-96.

Foster BL, Dastjerdi M, Parvizi J (2012) Neural populations in human posteromedial cortex display opposing responses during memory and numerical processing. Proc Natl Acad USA 109:15514-9.

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005) The human brain is intrinsically organized into dynamic anticorrelated functional networks. Proc Natl Acad Sci 102:9673-8

Fox MD, Zhang D, Snyder AZ, Raichle ME (2009) The global signal and observed anticorrelated resting state brain networks. J Neurophysiol 101(6):3270-83

Frankland PW, Bontempi B (2005) The organization of recent and remote memories. Nat Rev Neurosci 6:119-30.

Fried I, MacDonald KA, Wilson CL (1997) Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. Neuron, 18:753-65.

Fries P (2005) A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn Sci 9:474-80.

Fries P (2009) The model- and the data-gamma. Neuron 64:601-2

Friston KJ, Ashburner JT, Kiebel SJ, Nichols TE, Penny WD (2006) Statistical parametric mapping. London: Academic Press.

Friston KJ. Li B, Daunizeau J, Stephan KE. (2011) Network discovery with DCM. Neuroimage; 56:1202-21

Fuentemilla L, Penny WD, Cashdollar N, Bunzeck N, Duzel E (2010) Theta-coupled periodic replay in working memory. Curr Biol, 20:606-12.

Furtak SC, Ahmed OJ, Burwell RD (2012) Single neuron activity and theta modulation in postrhinal cortex during visual object discrimination. Neuron, 76:976-88

Gaffan D (2002) Against memory systems. Phil Trans R Soc Lond B 357:1111-1121

Gais S, Albouy G, Boly M, Dang-Vu TT, Darsaud A, Desseilles M, Rauchs G, Schabus M, Sterpenich V, Vandewalle G, Maquet P, Peigneux P (2007) Sleep transforms the cerebral trace of declarative memories. Proc Natl Acad Sci USA, 104:18778-83.

Gallagher M, Holland PC (1994) The amygdala complex: multiple roles in associative learning and attention. Proc Natl Acad Sci USA, 91(25):11771-6.

George S, Mufson EJ, Leurgans S, Shah RC, Ferrari C, deToledo-Morrell L (2011) MRI-based volumetric measurement of the substantia innominata in amnestic MCI and mild AD. Neurobiol Aging, 32:1756-64

Georges-Francois P, Rolls ET, Robertson RG (1999) Spatial view cells in the primate hippocampus: allocentric view not head direction or eye position or place. Cereb Cortex 3:197-212

Girardeau G, Benchenane K, Wiener SI, Buzsaki G, Zugaro MB (2009) Selective suppression of hippocampal ripples impairs spatial memory. Nat Neurosci, 12:1222-23

Gonsalves BD, Kahn I, Curran T, Norman KA, Wagner AD (2005) Memory strength and repetition suppression: multimodal imaging of medial temporal cortical contributions to recognition. Neuron 47: 751–761.

Good MA, Barnes P, Staal V, McGregor A, Honey RC (2007) Context- but not familiarity-dependent forms of object recognition are impaired following excitotoxic hippocampal lesions in rats. Behav Neuro 121:218-223

Gould NF, Holmes MK, Fantie BD, Luckenbaugh DA, Pine DS, Gould TD, Burgess N, Manji HK, Zarate CA Jr (2007) Performance on a virtual reality spatial memory navigation task in depressed patients. Am J Psychiatry 164: 516–519.

Grastyan E, Lissak K, Madarasz I, Donhoffer H (1959) Hippocampal electrical activity during the development of conditioned reflexes. Electroencephalogr Clin Neurophysiol 11:409–430.

Gray CM, Singer W (1989) Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. Proc Natl Acad Sci USA, 86:1698-1702.

Gray CM, König P, Engel AK, Singer W (1989) Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. Nature 338(6213):334-7

Gray JA (1982) The neuropsychology of anxiety: an enquiry into the functions of the septo-hippocampal system. Oxford: Oxford University Press. 548 p.

Griesmayr B, Gruber WR, Klimesch W, Sauseng P (2010) Human frontal midline theta and its synchronization to gamma during a verbal delayed match to sample task. Neurobiol Learn Mem 93:208-15.

Gross J, Kujala J, Hamalainen M, Timmermann L, Schnitzler A, Salmelin R (2001) Dynamic imaging of coherent sources: studying neural interactions in the human brain. Proc Natl Acad Sci USA 98(2):694-9

Gross J, Baillet S, Barnes GR, Henson RN, Hillebrand A, Jensen O, Jerbi K, Litvak V, Maess B, Oostenveld R, Parkkonen L, Taylor JR, van Wassenhove V, Wibral M, Schoffelen JM (2013) Good practice for conducting and reporting MEG research. Neuroimage 65:349-63

Grunwald T, Lehnertz K, Heinze HJ, Helmstaedter C, Elger CE (1998) Verbal novelty detection within the human hippocampus proper. Proc Natl Acad Sci USA, 95:3193-7

Guderian S, Duzel E (2005) Induced theta oscillations mediate large-scale synchrony with mediotemporal areas during recollection in humans. Hippocampus 15:901-12

Guderian S, Schott BH, Richardson-Klavehn A, Duzel E (2009) Medial temporal theta state before an event predicts episodic encoding success in humans. Proc Natl Acad Sci USA 106:5365-70

Gupta AS, van der Meer MA, Touretzky DS, Redish AD (2012) Segmentation of spatial experience by hippocampal theta sequences. Nat Neurosci 15(7):1032-9

Gureckis TM, Markant DB (2012) Self-direct learning: a cognitive and computational perspective. Perspectives on Psychological Science 7:464-81

Guitart-Masip M, Barnes GR, Horner A, Bauer M, Dolan RJ, Duzel E (2013) Synchronization of medial temporal lobe and prefrontal rhythms in human decision making. J Neurosci 33:442-51

Habas C, Kamdar N, Nguyen D, Prater K, Beckmann CF, Menon V, Greicius MD (2009) Distinct cerebellar contributions to intrinsic connectivity networks. J Neurosci 29: 8586–8594

Hafting T, Fyhn M, Molden S, Moser MB, Moser EI (2005) Microstructure of a spatial map in the entorhinal cortex. Nature 436:801-6

Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, Sporns O (2008) Mapping the structural core of human cerebral cortex. PLoS Biol 6:e159

Halgren E, Babb Tl, Crandall PH (1978) Human hippocampal formation EEG desynchronizes during attentiveness and movement. Electroencephalogr Clin Neurophysiol 44:778-81.

Halgren E, Squires NK, Wilson CL, Rohrbaugh JW, Babb TL, Crandall PH (1980) Endogenous potentials generated in the human hippocampal formation and amygdala by infrequent events. Science 210:803–805.

Hall SD, Holliday IE, Hillebrand A, Singh KD, Furlong PL, Hadjipapas A, Barnes GR (2005) The missing link: analogous human and primate cortical gamma oscillations. Neuroimage 26:13-7.

Hamani C, McAndrews MP, Cohn M, Oh M, Zumsteg D, Shapiro CM, Wennberg RA, Lozano AM (2008) Memory enhancement induced by hypothalamic/fornix deep brain stimulation. Ann Neurol 63:119-23.

Handwerker DA, Roopchansingh V, Gonzalez-Castillo J, Bandettini PA (2012) Periodic changes in fMRI connectivity. Neuroimage 63:1712-9.

Hansen P, Kringelbach M, & Salmelin (2010) MEG: An introduction to methods. Oxford University Press p. 448

Hassabis D, Kumaran D, Vann S, Maguire EA (2007) Patients with hippocampal amnesia cannot imagine new experiences. Proc. Natl. Acad. Sci. USA104, 1726–1731

Hassabis D, Maguire EA (2007) Deconstructing episodic memory with construction. Trends Cogn Sci 11:299-306.

Hasson U, Nusbaum HC, Small SL (2009) Task-dependent organization of brain regions active during rest. Proc Natl Acad Sci USA 106:10841-6.

Harvey C. D, Collman F, Dombeck D. A, Tank D. W (2009) Intracellular dynamics of hippocampal place cells during virtual navigation. Nature 461: 941–946.

Hasselmo ME (1995) Neuromodulation and cortical function: modelling the physiological basis of behavior. Behav Brain Res 67:1-27.

Hasselmo M, Bodelon C, Wyble BP (2002) A proposed function for hippocampal theta rhythm: separate phases of encoding and retrieval enhance reversal of prior learning. Neural Comput 14: 793-817.

Hasselmo M (2005) Expecting the unexpected: modelling of neuromodulation. Neuron 46:526-8

He BJ, Zempel JM, Snyder AZ, Raichle ME: The temporal structures and functional significance of scale-free brain activity. Neuron 2010, 66:353-69.

Heeger DJ, Ress D (2002) What does fMRI tell us about neuronal activity? Nat Rev Neurosci 3(2):142-51

Hermann C, Munk M, Engel A. (2004) Cognitive functions of gamma-band activity: memory match and utilization. Trends Cogn Sci 8:347-355.

Hesselmann, G., Kell, C. A., and Kleinschmidt, A. (2008a) Ongoing activity fluctuations in hMT+ bias the perception of coherent visual motion. J Neurosci 28:14481–14485.

Hesselmann, G., Kell, C. A., Eger, E., and Kleinschmidt, A. (2008b) Spontaneous local variations in ongoing neural activity bias perceptual decisions. Proc Natl Acad USA 105:10984–10989.

Hipp JF, Hawellek DJ, Corbetta M, Siegel M, Engel AK (2012) Large-scale cortical correlation structure of spontaneous oscillatory activity. Nat Neurosci 15:884-90

Hoffmann L. C, Berry S. D (2009) Cerebellar theta oscillations are synchronized during hippocampal theta-contingent trace conditioning. Proc Natl Acad Sci USA 106: 21371–21376.

Holland PC, Gallagher M (2006) Different roles from amygdala central nucleus and substantia innominata in the surprise-induced enhancement of learning. J Neurosci 26:3791-3797.

Hoogenboom N, Schoffelen JM, Oostenveld R, Parkes LM, Fries P (2006) Localizing human visual gamma-band activity in frequency, time and space. Neuroimage 29:764-73.

Hori E, Tabuchi E, Matsumura N, Tamura R, Eifuku S, Endo S, Nishijo H, Ono T (2003) Representation of place by monkey hippocampal neurons in real and virtual translocation. Hippocampus 13:190-6

Hori E, Nishio Y, Kazui K, Umeno K, Tabuchi E, Sasaki K, Endo S, Ono T, Nishijo H (2005) Place-related neural responses in the monkey hippocampal formation in a virtual space. Hippocampus 15:991-6

Howard LR, Kumaran D, Olafsdottir HF, Spiers HJ (2011) Double dissociation between hippocampal and parahippocampal responses to object-background context and scene novelty. J Neurosci 31:5253-61.

Huettel SA, Song AW, McCarthy G (2009) Functional magnetic resonance imaging. Sunderland, United States: Sinauer Associates.

Hull CL (1935) The conflicting psychologies of learning: a way out. Psychological Review 42:491-516

Hutton C, Bork A, Josephs O, Deichmann R, Ashburner J, Turner R (2002). Image distortion correction in fMRI: A quantitative evaluation. Neuroimage 16: 217-240.

Hyman JM, Zilli EA, Paley AM, Hasselmo ME (2005) Medial prefrontal cortex cells show dynamic modulation with the hippocampal theta rhythm dependent on behaviour. Hippocampus 15:739-49.

Hyman JM, Hasselmo ME, Seamans JK (2011) What is the functional relevance of prefrontal cortex entrainment to hippocampal theta rhythms. Front Neurosci 4:24.

Iaria G, Petrides M, Dagher A, Pike B, Bohbot VD (2003) Cognitive strategies dependent on the hippocampus and caudate nucleus in human navigation: variability and change with practice. J Neurosci 23:5945-52.

Igloi K, Doeller CF, Berthoz A, Rondi-Reig L, Burgess N (2010) Lateralized human hippocampal activity predicts navigation based on sequence or place memory. Proc Natl Acad Sci USA 107:14466-71.

Irmis F (1974) Relation between rhythmical hippocampal ("theta") and olfactory (breath) EEG activity during spontaneous behaviour and REM sleep in rats. Act Nerv Super (Praha) 16:96-7.

Ishihara T, Hayashi H, Hishikawa Y (1981) Distribution of frontal midline theta rhythm (FmO) on the scalp in different states (mental calculation, resting and drowsiness). EEG Clinical Neurophysiology 52:S19.

Ishii R, Shinosaki K, Ukai S, Inouye T, Ishihara T, Yoshimine T, Hirabuki N, Asada H, Kihara T, Robinson SE, Takeda M (1999) Medial prefrontal cortex generates frontal midline theta rhythm. Neuroreport 10:675-679.

Jacobs J, Kahana M. J (2010) Direct brain recordings fuel advances in cognitive electrophysiology. Trends Cog Sci 14: 162–171.

Jacobs J, Korolev I, Caplan J, Ekstrom A, Litt B, Baltuch G, et al. (2010) Right-lateralized brain oscillations in human spatial navigation. J Cogn Neurosci 22:824–36.

Jacobs J, Kahana MJ, Ekstrom AD, Mollison MV, Fried I (2010) A sense of direction in human entorhinal cortex. Proc Natl Acad Sci USA 107:6487-92.

Jadhav SP, Kemere C, German PW, Frank LM (2012) Awake hippocampal sharp-wave ripples support spatial memory. Science 336:1454-8

Janzen G, van Turennout M (2004).Selective neural representation of objects relevant for navigation. Nat. Neurosci 7:673–677.

Jeewajee A, Lever C, Burton S, O'Keefe J, Burgess N (2008) Environmental novelty is signaled by reduction of the hippocampal theta frequency. Hippocampus 18: 340–348.

Jensen O, Lisman JE (1996) Hippocampal CA3 region predicts memory sequences: accounting for the phase precession of place cells. Learn Mem 3:279-287.

Jensen O, Tesche C. D (2002) Frontal theta activity in humans increases with memory load in working memory task. Eur J Neurosci 15: 1395–1399.

Jensen O, Colgin L (2007) Cross-frequency coupling between neural oscillations. Trends Cogn Sci 11:267-269.

Jensen O, Kaiser J, Lachaux J (2007) Human gamma-frequency oscillations associated with attention and memory. Trends Neurosci 30:317-24.

Johnson A, Redish AD (2007) Neural ensembles in CA3 transiently encode paths forward of the animal at a decision point. J Neurosci 27:12176-89

Jones MW, Wilson MA (2005a) Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. PLoS Biol e402.

Jones MW, Wilson MA (2005b) Phase precession of medial prefrontal cortical activity relative to the hippocampal theta rhythm. Hippocampus 15:867-73

Jutras MJ, Buffalo EA (2009) Gamma-band synchronization in the macaque hippocampus and memory formation. J Neurosci 29:12521-31

Jutras MJ, Buffalo EA (2010) Synchronous neural activity and memory formation. Curr Opin Neurobiol 20:150-5

Kahana MJ, Sekuler R, Caplan JB, Kirschen M, Madsen JR (1999) Human theta oscillations exhibit task dependence during virtual maze navigation. Nature 399:781-784

Kelemen E, Moron I, Fenton AA (2005) Is the hippocampal theta rhythm related to cognition in a non-locomotor place recognition task? Hippocampus 15: 472–479

Kensinger EA, Addis DR, Atapattu RK (2011) Amgydala activity at encoding corresponding with memory vividness and with memory for select episodic details. Neuropsychologia 49:663-73.

Kesner RP (2000) Behavioral analysis of the contribution of the hippocampus and paritetal cortex to the processing of information: interactions and dissociations. Hippocampus 10:483-90.

King JA, Blair RJ, Mitchell DG, Dolan RJ, Burgess N (2006) Doing the right thing: a common neural circuit for appropriate violent or compassionate behaviour. Neuroimage 30:1069-76.

Klimesch W (1996) Memory processes, brain oscillations and EEG synchronization. Int J Psychophysiol 24: 61–100.

Klimesch W, Doppelmayr M, Russegger H, Pachinger T (1996) Theta band power in the human scalp EEG and the encoding of new information. Neuroreport 17: 1235–1240.

Klimesch W, Doppelmayr M, Stadler W, Pollhuber D, Sauseng P, Rohm D (2001) Episodic retrieval is reflected by a process specific increase in human electroencephalographic theta activity. Neurosci Lett 302:49-52.

Koenig J, Linder AN, Leutgeb JK, Leutgeb S (2011) The spatial periodicity of grid cells is not sustained during reduced theta oscillations. Science 332:592-5

Knight R (1996) Contribution of human hippocampal region to novelty detection. Nature 383:256-9.

Kohler S, Danckert S, Gati JS, Menon RS (2005) Novelty responses to relational and non-relational information in the hippocampus and the parahippocampal region: a comparison based on event-related fMRI. Hippocampus 15:763-74.

Kramis R, Vanderwolf CH, Bland BH (1975) Two types of hippocampal rhythmical slow activity in both the rabbit and the rat: relations to behaviour and effects of atropine, diethyl ether, urethane, and pentobarbital. Exp Neurol 49:58-85.

Kravitz, D.J., Peng, C.S., Baker, C.I. (2011). Real-world scene representations in high-level visual cortex: It's the spaces more than the places. J. Neurosci 31:7322–7333.

Kravitz DJ, Saleem, KS, Baker CI, Mishkin, M (2011). A new neural framework for visuospatial processing. Nat Rev Neurosci 12:217–230

Kriegeskorte N, Mur M, Ruff D, Kiani R, Bodurka J, Esteky H, Tanaka H, Bandettini, PA (2008). Matching categorical object representations in inferior temporal cortex of man and monkey. Neuron 60:1126–1141.

Krienen FM, Buckner RL (2009) Segregated fronto-cerebellar circuits revealed by intrinsic functional connectivity. Cereb Cortex 19: 2485–2497.

Kumaran D, Maguire EA (2006) An unexpected sequence of events: mismatch detection in the human hippocampus. PLoS Biol 4:e424.

Kumaran D, McClelland JL (2012) Generalziation through the recurrent interaction of episodic memories: a model of the hippocampal system. Psychol Rev 119:573-616.

Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R, Cheng HM, Brady TJ, Rosen BR (1992) Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci USA 89:5675-9

Lachaux J, Rodriguez E, Martiniere J, Varela F (1999) Measuring phase synchrony in brain signals. Hum Brain Mapp 8:194–208.

Lakatos P, Shah AS, Knuth KH, Ulbert I, Karmos G, Schroeder CE (2005) An oscillatory hierarchy controlling neuronal excitiability and stimulus processing in the auditory. J Neurophysiol 94:1904-11.

Lakatos P, Karmos G, Mehta AD, Ulbert I, Schroeder CE (2008) Entrainment of neuronal oscillations as a mechanism of attentional selection. Science 320:110-3.

Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, Wherrett J, Naglie G, Hamani C, Smith GS, Lozano AM (2010) A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. Ann Neurol 68:521-34.

Lederborgen F, Kirsch P, Haddad L, Streit F, Tost H, Schuch P, Wust S, Pruessner JC, Rietschel M, Deuschle M, Meyer-Lindenberg A (2011) City living and urban upbringing affect neural social stress processing in humans. Nature 474:498-501.

Lee H, Simpson GV, Logothetis NK, Rainer G (2005) Phase locking of single neuron activity to theta oscillations during working memory in monkey extrastriate visual cortex. Neuron 45:147-56.

Lee I, Hunsaker MR, Kesner RP (2005) The role of hippocampal subregions in detecting spatial novelty. Behav Neurosci 119: 145–153.

Lega BC, Jacobs J, Kahana M (2012) Human hippocampal theta oscillations and the formation of episodic memories. Hippocampus 22:748-61.

Lesburguères E, Gobbo OL, Alaux-Cantin S, Hambucken A, Trifilieff P, Bontempi B (2011) Early tagging of cortical networks is required for the formation of enduring associative memory. Science 331

Le Van Quyen M, Staba R, Bragin A. Dickson C, Valderrama M, Fried I, Engel J (2010) Large-scale microelectrode recordings of high-frequency gamma oscillations in human cortex during sleep. J Neurosci 30:7770-82.

Lever C, Wills T, Cacucci F, Burgess N, O'Keefe J (2002) Long-term plasticity in hippocampal place-cell representation of environmental geometry. Nature 416:90-94.

Lever C, Burton S, Jeewajee, A, O'Keefe J, Burgess, N (2009). Boundary vector cells in the subiculum of the hippocampal formation. J. Neurosci. 29, 9771–9777.

Lever C, Burton S, Jeewajee A, Wills TJ, Cacucci F, Burgess N, O'Keefe, J. (2010). Environmental novelty elicits a later theta phase of firing in CA1 but not subiculum. Hippocampus 20:229-234.

Lever C, Kaplan R, Burgess N (In Press) 'The function of oscillations in the hippocampal formation' in Space, Time, and Memory in the Hippocampal Formation. eds: Derdikman D & Knierim J

Lewis CM, Baldassarre A, Committeri G, Romani GL, Corbetta M (2009) Learning sculpts the spontaneous activity of the resting human brain. Proc Natl Acad Sci USA 106:17558-63.

Liebe S, Hoerzer GM, Logothetis NK, Rainer G (2012) Theta coupling between V4 and prefrontal cortex predicts visual short-term memory performance. Nat Neuro 15:456-62.

Lisman J. E, Idiart M. A (1995) Storage of 7+/−2 short-term memories in oscillatory subcycles. Science 267:1512–1515.

Lin SC, Nicolelis MA (2008) Neuronal ensemble bursting in the basal forebrain encodes salience irrespective of valence. Neuron 59:138-49.

Lisman J, Buzsaki G (2008) A neural coding scheme formed by the combined function of gamma and theta oscillations. Schizophr Bull 34:974-80.

Litvak V, Mattout J, Kiebel S, Phillips C, Henson R, Kilner J, Barnes G, Oostenveld R, Daunizeau J, Flandin G, Penny W, Friston K (2011) EEG and MEG data analysis in SPM8. Comput Intell Neurosci 2011:852961.

Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. Nature 412:150-7.

Logothetis NK (2002) The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. Philos Trans R Soc Lond B Biol Sci 357:1003-37

Logothetis NK, Eschenko O, Murayama Y, Augath M, Steudel T, Evrard HC, Besserve M, Oeltermann A (2012) Hippocampal-cortical interaction during periods of subcortical silence. Nature 491:547-53.

Luczak A, Bartho P, Marguet SL, Buzsåki G, Harris KD (2007) Sequential structure of neocortical spontaneous activity in vivo. Proc Natl Acad Sci USA 104:347-52.

Luczak A, Bartho P, Harris KD (2009) Spontaneous events outline the realm of possible sensory responses in neocortical populations. Neuron 62:413-25.

Luczak A, Maclean JN (2012) Default activity patterns at the neocortical microcircuit level. Front Integr Neurosci 6-30.

Ludmer R, Dudai Y, Rubin N (2011) Uncovering camouflage: amygdala activation predicts long-term memory of induced perceptual insight. Neuron 69:1002-14.

Maguire EA Mummery CJ (1999) Differential modulation of a common memory retrieval network revealed by positron emission tomography. Neuroreport 9:54-61.

Maguire EA, Gadian DG, Johnsrude IS, Good CD, Ashburner J, Frackowiak RS, Frith CD (2000) Navigation-related structural change in the hippocampi of taxi drivers. Proc Natl Acad Sci USA 97:4398-403.

Manelis A, Reder LM, Hanson SJ (2012) Dynamic changes in the medial temporal lobe during incidental learning of object-location associations. Cereb Cortex 22:828-37.

Mansfield P (1977) Multi-planar image formation using NMR spin echoes. J Phys C, 10:L55-8.

Maris E, van Vugt M, Kahana M (2011) Spatially distributed patterns of oscillatory coupling between high-frequency amplitudes and low-frequency phases in human iEEG. Neuroimage 54:836-50.

Marr D (1971). Simple Memory - Theory for Archicortex. Philosophical Transactions of the Royal Society of London Series B 262:23-81.

Marshall L, Born J (2007) The contribution of sleep to hippocampus-dependent memory consolidation. Trends Cogn Sci 11:442-50.

Martin A (1999) Automatic activation of the medial temporal lobe during encoding lateralized influences of meaning and novelty. Hippocampus 9:62-70.

Mattfield AT, Stark CE (2011) Striatal and medial temporal lobe functional interactions during visuomotor associative learning. Cereb Cortex 21: 647–658.

McHugh SB, Fillenz M, Lowry JP, Rawlins JN, Bannerman DM (2011) Brain tissue oxygen amperometry in behaving rats demonstrates functional dissociation of dorsal and ventral hippocampus during spatial processing and anxiety. Eur J Neurosci 33:322-37.

Meltzer JA, Fonzo GA, Constable RT (2009) Transverse patterning dissociates human EEG theta power and hippocampal BOLD activation. Psychophysiol 46: 153–162.

Middleton SJ, Racca C, Cunningham MO, Traub RD, Monyer H, Knopfel T, Schofield IS, Jenkins A, Whittington MA (2008) High-frequency network oscillations in cerebellar cortex. Neuron 58:763-74.

Miller R (1989) Cortico-hippocampal interplay: self-organizing phase-locked loops for indexing memory. Psychobiology 17:115-28.

Mills T, Lalancette M, Moses SN, Taylor MJ, Quraan MA (2012) Techniques for detection and localization of weak hippocampal and medial frontal sources using beamformers in MEG. Brain Topogr 25:248-63.

Mitchell DJ, McNaughton N, Flanagan D, Kirk IJ (2008) Frontal-midline theta from the perspective of hippocampal ‘theta’. Prog Neurobiol 86:156-85.

Mizuseki K, Sirota A, Pastalkova E, Buzsaki G (2009) Theta oscillations provide temporal windows for local circuit computation in the entorhinal-hippocampal loop. Neuron 64:267-80

Montgomery SM, Buzsaki G (2007) Gamma oscillations dynamically couple hippocampal CA3 and CA1 regions during memory task performance. Proc Natl Acad Sci USA 104:14495-500.

Montogomery SM, Sirota A, Buzsaki G (2008) Theta and gamma coordination of hippocampal networks during waking and rapid eye movement sleep. J Neurosci 28:6731-41.

Morcom AM, Fletcher PC (2007) Does the brain have a baseline? Why we should be resisting a rest. Neuroimage 37:1073-1082

Morgan HM, Muthukumarawamy SD, Hibbs CS, Shapiro KL, Bracewell RM, Singh KD, Linden DEJ (2011) Feature integration in visual working memory: parietal gamma activity is related to cognitive coordination. J Neurophysiol 106:3185-94.

Mormann F, Fell J, Axmacher N, Weber B, Lehnertz K, Elger CE, Fernández G (2005) Phase/amplitude reset and theta-gamma interaction in the medial temporal lobe during a continuous word recognition memory task. Hippocampus 15:890-900.

Mormann F, Osterhage H, Andrzejak RG, Weber B, Fernández G, Fell K, Elger CE, Lehnertz K (2008) Independent delta/theta rhythms in the human hippocampus and entorhinal cortex. Front Hum Neurosci, 2:3.

Morris R (1984) Developments of a water-maze procedure for studying spatial learning in the rat. J Neurosci Methods, 11:47-60.

Morris R (2006) Theories of hippocampal function. In: Andersen P, Morris R. M, Amaral D. G, Bliss T. V. P, O'Keefe J, editors. The hippocampus book. New York: Oxford University Press. pp. 581–715.

Morrison SE, Salzman CD (2010) Re-valuing the amygdala. Curr Opin Neurobiol, 20:221-30.

Moses SN, Sutherland RJ, McDonald RJ (2002) Differential involvement of amygdala and hippocampus in responding to novel objects and contexts. Brain Res Bull 58:517-27.

Moses SN, Cole C, Driscoll I, Ryan JD (2005) Differential contributions of hippocampus, amygdala and perirhinal cortex to recognition of novel objects, contextual stimuli and stimulus relationships. Brain Res Bull 67:62-76.

Mullally SL, Maguire EA (2011) A new role for the parahippocampal cortex in representing space. J. Neurosci 31:7441–7449.

Murakami S, Okada Y (2006) Contributions of principal neocortical neurons to magnetoencephalography and electroencephalography signals. J Physiol 575:925-36.

Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA (2009) The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? Neuroimage 44(3):893-905.

Murray EA, Bussey TJ, Saksida LM (2007) Visual perception and memory: a new view of medial temporal lobe function in primates and rodents. Annu Rev Neurosci 30:99-122.

Muthukumaraswamy SD, Singh KD (2011) A cautionary note on the interpretation of phase-locking estimates with concurrent changes in power. Clin Neurophysiol, 122:2324-5.

Nadel L, Samsonovich A, Ryan L, Moscovitch M (2000) Multiple trace theory of human memory: computational, neuroimaging, and neuropsychological results. Hippocampus 10:352-68.

Nieuwenhuis IL, Takashima A, Oostenveld R, McNaughton BL, Fernández G, Jensen O (2012) The neocortical network representing associative memory reorganizes with time in a process engaging the anterior temporal lobe. Cereb Cortex 22:2622-33.

Nolte G, Curio G (2000) Current multipole expansion to estimate lateral extent of neuronal activity: a theoretical analysis. IEEE Trans Biomed Eng 10:1347-55.

Nyberg L (2005) Any novelty in hippocampal formation and memory? Curr Opin Neurol 18:424-8.

Nyhus E, Curran T (2010) Functional role of gamma and theta oscillations in episodic memory. Neurosci Biobehav Rev 34:1023-35

O'Keefe J, Bouma H (1969) Complex sensory properties of certain amygdala units in the freely moving cat. Exp Neurol 23:384-98.

O'Keefe J, Nadel L (1978). Hippocampus as a cognitive map. New York: Oxford UP.

O'Keefe J, Recce M, O'Keefe J (1993) Phase relationship between hippocampal place units and the EEG theta rhythm. Hippocampus 3:317-30.

O'Keefe J (2006) Hippocampal neurophysiology in the behaving animal. In: Andersen P, Morris R. M, Amaral D. G, Bliss T. V. P, O'Keefe J, editors. The hippocampus book. New York: Oxford University Press. pp. 475–548.

Ogawa S, Tank DW, Menon R, Ellerman JM, Kim SG, Merkle H, Ugurbil K (1992) Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci USA 89:5951

Olsen RK, Nichols EA, Chen J, Hunt JF, Glover GH, Gabrieli JD, Wagner AD (2009) Permormance-related sustained and anticipatory activity in human medial temporal lobe during delayed match-to-sample. J Neurosci 29:11880-90.

Oostenveld R, Fries P, Maris E, Schoffelen J-M (2011) FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. Computational Intelligence and Neuroscience 2011:156869.

Osipova D, Takashima A, Oostenveld R, Fernández G, Maris E, Jensen O (2006) Theta and gamma oscillations predict encoding and retrieval of declarative memory. J Neurosci 26:7523–7531.

Osipova D, Hermes D, Jensen O (2008) Gamma power is phase-locked to posterior alpha activity. PLoS One 3:e3990

Otten LJ, Quayle AH, Akram S, Ditewig TA, Rugg MD (2006) Brain activity before an event predicts later recollection. Nat Neurosci 9:489-91.

Owen AM, Milner B, Petrides M, Evans AC (1996) Memory for object features versus memory for object location: a positron-emission tomography study of encoding and retrieval processes. Proc Natl Acad Sci USA 93:9212-7

Paller K, Wagner AD (2002) Observing the transformation of experience into memory. Trends Cog Sci 6:93–102.

Papez JW (1937) A proposed mechanism of emotion. Arch Neurol Psychiatry 38:725-43.

Park H, Rugg MD (2010) Prestimulus hippocampal activity predicts later recollection. Hippocampus 20:24-28.

Park S, Brady TF, Greene MR, Oliva A (2011) Disentangling scene content from spatial boundary: complementary roles for the parahippocampal place area and lateral occipital complex in representing real-world scenes. J. Neurosci 31:1333–40.

Pastalkova E, Itskov V, Amarasingham A, Buzsaki G (2008) Internally generated cell assembly sequences in the rat hippocampus. Science 321:1322-7

Peigneux P, Orban P, Balteau E, Degueldre C, Luxen A, Laureys S, Maquet P (2006) Offline persistence of memory-related cerebral activity during active wakefulness. PLoS Biol 4:e100.

Pennartz CMA, Ito R, Verschure PFMJ, Battaglia FP, Robbins TW (2011) The hippocampal-striatal axis in learning, prediction and goal-directed behaviour. Trends Neurosci 34:548-559.

Penny WD, Duzel E, Miller KJ, Ojemann JG (2008) Testing for nested oscillations. J Neurosci Meth 174:50-61

Petridou N, Plenz D, Silva AC, Loew M, Bodurka J, Bandettini PA (2006) Direct magnetic resonance detection of neuronal electrical activity. Proc Natl Acad Sci USA 103:16015-20.

Phelps EA, LeDoux JE (2005) Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron 48:175-87.

Phelps EA (2006) Emotion and cognition: insights from studies of the human amygdala. Annu Rev Psychol 57:27-53.

Pihlajamaki M, Tanila H, Hanninen T, Kononen M, Mikkonen M, Jalkanen V, Partanen K, Aronen HJ, Soininen H (2003) Encoding of novel picture pairs activates the perirhinal cortex: an fMRI study. Hippocampus 13:67-80.

Poch C, Fuentemilla L, Barnes GR, Duzel E (2011) Hippocampal theta-phase modulation of replay correlates with configural-relational short-term memory performance. J Neurosci 31:7038-42.

Poldrack RA, Mumford JA, Nichols TE (2011) Handbook of functional MRI data analysis. New York: Cambridge UP.

Preston AR, Bornstein AM, Hutchinson JB, Gaare ME, Glover GH, Wagner AD (2010) High-resolution fMRI of content-sensitive subsequent memory responses in human medial temporal lobe. J Cogn Neurosci 22:156-73.

Quraan MA, Moses SN, Hung Y, Mills T, Taylor MJ (2011) Detection and localization of hippocampal activity using beamformers with MEG: a detailed investigation using simulations and empirical data. Hum Brain Mapp 32:812-27.

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. Proc Natl Acad Sci USA 98:676-82. prompt declarative memory consolidation. Science 315:1426-9.

Raghavachari S, Kahana MJ, Rizzuto DS, Caplan JB, Kirschen MP, Bourgeois B, Madsen JR, Lisman JE (2001) Gating of human theta oscillations by a working memory task. J Neurosci 21:3175-83.

Ramadan W, Eschenko O, Sara SJ (2009) Hippocampal sharp wave/ripples during sleep for consolidation of associative memory. PLoS One 4:e6697

Ranganath C, Rainer G (2003) Neural mechanisms for detecting and remembering novel events. Nat Rev Neurosci 4:193-202

Ranganath C, Ritchey M (2012) Two cortical systems for memory-guided behaviour. Nat Rev Neurosci 13:713-26

Rasch B, Buchel C, Gais S, Born J (2007) Odor cues during slow-wave sleep prompt declarative memory consolidation. Science 315:1426-9

Riggs L, Moses SN, Bardouille T, Herdman AT, Ross B, Ryan JD (2009) A complementary analytic approach to examining medial temporal lobe sources using magnetoencephalography. Neuroimage 45:627-42.

Robinson SE (2004) Localization of event-related activity by SAM(erf). Neurol Clin Neurophysiol 2004:109

Rolls ET, Robertson RG, Georges-Francois P (1997) Spatial view cells in the primate hippocampus. Eur J Neurosci 8:1789-94

Rugg MD, Coles MG: Electrophysiology of Mind: Event-Related Potentials and Cognition. Oxford: O.U.P, 1996.

Rushworth MF, Noonan MP, Boorman ED, Walton ME, Behrens TE (2011) Frontal cortex and reward-guided learning and decision-making. Neuron 70:1054-69

Rutishauser U, Mamelak AN, Schuman EM (2006) Single-trial learning of novel stimuli by individual neurons of the human hippocampus-amygdala complex. Neuron 49:805–813.

Rutishauser U, Ross IB, Mamelak AN, Schuman EM (2010) Human memory strength is predicted by theta-frequency phase-locking of single neurons. Nature 464:903-7.

Sato N, Ozaki TJ, Someya Y, Anami K, Ogawa S, Mizuhara H, Yamaguchi Y (2010) Subsequent memory-dependent EEG theta correlates to parahippocampal blood oxygenation level-dependent response. Neuroreport 21:168-72.

Sauseng P, Griesmayr B, Freunberger R, Klimesch W (2010) Control mechanisms in working memory: a possible function of EEG theta oscillations. Neurosci Biobehav Rev 34:1015-22.

Save E, Buhot MC, Foreman N, Thinus-Blanc C (1992a) Exploratory activity and response to a spatial change in rats with hippocampal or posterior parietal cortical lesions. Behav Brain Res 47:113–127.

Save E, Poucet B, Foreman N, Buhot MC (1992b) Object exploration and reactions to spatial and nonspatial changes in hooded rats following damage to parietal cortex or hippocampal formation. Behav Neurosci 106:447–456.

Schacter DL, Addis DR, Buckner RL (2007) Remembering the past to imagine the future: the prospective brain. Nat Rev Neurosci 8:657-61

Schapiro AC, Kustner LV, Turk-Browne NB (2012) Shaping of object representations in the human medial temporal lobe based on temporal regularities. Curr Biol 22:1622-7.

Schon K, Hasselmo ME, Lopresti ML, Tricarico MD, Stern CE (2004) Persistence of parahippocampal representation in the absence of stimulus input enhances long-term encoding: a functional magnetic resonance imaging study of subsequent memory after a delayed match-to-sample task. J Neurosci 24:11088-97

Schroeder CE, Lakatos P (2009a) The gamma oscillation: master or slave? Brain Topogr 22:24-6.

Schroeder CE, Lakatos P. (2009b) Low-frequency neuronal oscillations as instruments of sensory selection. Trends Neurosci 32:9-18.

Scoville W, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry, 20:11-21.

Sederberg PB, Kahana MJ, Howard MW, Donner EJ, Madsen JR (2003) Theta and gamma oscillations during encoding predict subsequent recall. J Neurosci 23: 10809–14.

Sederberg PB, Schulze-Bonhage A, Madsen JR, Bromfield EB, Mc Carthy DC, Brandt A, Tully MS, Kahana MJ (2007) Hippocampal and neocortical gamma oscillations predict memory formation in humans. Cereb Cortex 17:1190-6.

Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. (2009) Neurodegenerative diseases target large-scale human brain networks. Neuron 62:42-52.

Seidenbecher T, Laxmi TR, Stork O, Pape HC (2003) Amygdalar and hippocampal theta rhythm synchronization during fear memory retrieval. Science 301: 846–850.

Siegel M, Warden MR, Miller EK (2009) Phase-dependent neuronal coding of objects in short-term memory. Proc Natl Acad Sci USA 106:21341-6

Sekihara K, Nagarajan SS, Poeppel D, Marantz A (2004) Asymptotic SNR of scalar and vector minimum-variance beamformers for neuromagnetic source reconstruction. IEEE Trans Biomed Eng, 51:1726–1734.

Seymour B, Dolan R (2008) Emotion, decision making, and the amygdala. Neuron 58:662-71

Sheth A, Berretta S, Lange N, Eichenbaum H (2008) The amygdala modulates neuronal activation in the hippocampus in response to spatial novelty. Hippocampus 18:169-81.

Shin J (2011) The interrelationship between movement and cognition: theta rhythm and the P300 event-related potential. Hippocampus 21:744–752.

Siapas AG, Lubenov EV, Wilson MA (2005) Prefrontal phase locking to hippocampal theta oscillations. Neuron 46:141-51.

Singer W, Gray CM (1995) Visual feature integration and the temporal correlation hypothesis. Annu Rev Neurosci 18:555-86.

Sirota A, Montgomery S, Fujisawa S, Isomura Y, Zugaro M, Buzsaki G (2008) Entrainment of neocortical neurons and gamma oscillations by the hippocampal theta rhythm. Neuron 60:683:97.

Skaggs WE, McNaughton BL, Wilson MA, Barnes CA (1996) Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. Hippocampus 6:159-72.

Skaggs WE, McNaughton BL (1996) Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. Science, 271:1870-3.

Skaggs WE, McNaughton BL, Permenter M, Archibeque M, Vogt J, Amaral DG, Barnes CA (2007) EEG sharp waves and sparse ensemble unit activity in the macaque hippocampus. J Neurophysiol, 98:898-910.

Sokolov EN (1963) Higher nervous functions; the orienting reflex. Annu Rev Physiol, 25:545-80.

Solstad, T., Boccara, C., Kropff, E., Moser, M.-B., Moser, E.I. (2008). Representation of geometric borders in the entorhinal cortex. Science 322:1865–1868.

Song EY, Kim YB, Kim YH, Jung MW (2005) Role of active movement in place-specific firing of hippocampal neurons. Hippocampus 15:8–17.

Spiers HJ, Burgess N, Maguire EA, Baxendale SA, Hartley T, Thompson PJ, O'Keefe J (2001) Unilateral temporal lobectomy patients show lateralized topographical and episodic memory deficits in a virtual town. Brain 124: 2476–2489.

Squire LR, Cohen NJ, Nadel L: The medial temporal region and memory consolidation: a new hypothesis, G. Weingartner, E. Parker, Editors , Memory Consolidation, Erlbaum, Hillsdale, NJ (1984), pp. 185–210.

Stam CJ, Nolte G, Daffertshofer A (2007) Phase lag index: assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. Hum Brain Map 28:1178-93.

Staresina BP, Duncan KD, Davachi L (2011) Perirhinal and parahippocampal cortices differentially contribute to later recollection of object- and scene-related event details. J Neurosci 31:8739-47.

Stark CE, Squire LR (2001) When zero is not zero: the problem of ambiguous baseline conditions in fMRI. Proc Natl Acad Sci USA 98:12760-6

Staudigl T, Hanslmayr S (2013) Theta oscillations at encoding mediate the context-dependent nature of human episodic memory. Curr Bio, EPub Advanced

Stern CE, Corkin S, Gonzalez RG, Guimaraes AR, Baker JR, Jennings PJ, Carr CA, Sugiura RM, Vedantham V, Rosen BR (1996) The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. Proc Natl Acad Sci USA 93:8660-5.

Stevens WD, Buckner RL, Schacter DL. (2010) Correlated low-frequency BOLD fluctuations in the resting human brain are modulated by recent experience in category-preferential visual regions. Cerebral Cortex 20:1997-2006.

Stewart M, Fox SE (1991) Hippocampal theta activity in monkeys. Brain Res 538:59-63

Strange BA, Duggins A, Penny W, Dolan RJ, Friston KJ (2005) Information theory, novelty and hippocampal responses: unpredicted or unpredictable? Neural Netw 18:225-30.

Super H, van der Togt C, Spekreijse H, Lamme VA (2003) Internal state of monkey primary visual cortex (V1) predicts figure-ground perception. J Neurosci 23:3407-14.

Suthana N, Haneef Z, Stern J, Mukamel R, Behnke E, Knowlton B, Fried I (2012) Memory enhancement and deep-brain stimulation of the entorhinal area. N Engl J Med 9:502-10.

Summerfield C, Mangels JA (2005) Coherent theta-band EEG activity predicts item-context binding during encoding. Neuroimage 24:692-703.

Takashima A, Petersson KM, Rutters F, Tendolkar I, Jensen O, Zwarts MJ, McNaughton BL, Fernández G (2006) Declarative memory consolidation in humans: A prospective functional magnetic resonance imaging study. Proc Natl Acad Sci USA 103:756-61.

Takashima A, Nieuwenhuis IL, Jensen O, Talamini LM, Rijpkema M, Fernández G (2009) Shift from hippocampal to neocortical centered retrieval network with consolidation. J Neurosci 29:10087-93.

Takashima A, Petersson KM, Rutters F, Tendolkar I, Jensen O, Zwarts MJ, McNaughton BL, Fernández G (2006) Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. Proc Natl Acad Sci USA 103:756-61.

Tambini A, Ketz N, Davachi L (2010) Enhanced brain correlations during rest are related to memory for recent experiences. Neuron 65:280-290.

Tallon-Baudry C, Bertrand O (1999) Oscillatory gamma activity in humans and its role in object representation. Trends Cogn Sci 3:151-62.

Taube JS, Muller RU, Ranck JB Jr (1990) Head-direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative analysis. J Neurosci 10:420-35.

Taylor C, Dudek F (1984) Excitation of hippocampal pyramidal cells by an electrical field effect. J Neurophysiol 52:126-42.

Tesche CD, Karhu J (2000) Theta oscillations index human hippocampal activation during a working memory task. Proc Natl Acad Sci USA 97:919-924.

Terrazas A, Krause M, Lipa P, Gothard KM, Barnes CA, McNaughton BL (2005) Self-motion and the hippocampal spatial metric. J Neurosci 25:8085-96.

Tesche CD, Karhu J (2000) Theta oscillations index human hippocampal activation during a working memory task. Proc Natl Acad Sci USA 97:919–924

Teyler TJ, DiScenna P (1986) The hippocampal memory indexing theory. Behav Neurosci, 100:147-54

Thoresen C, Jensen J, Sigvartsen NP, Bolstad I, Server A, Nakstad PH, Andreassen OA, Endestad T (2011) Arousal modulates activity in the medial temporal lobe during a short-time relation memory task. Front Hum Neurosci 5:177.

Tolman E: Cognitive maps in rats and men. 1948. In The Neurobiology of Learning and Memory. Edited by Shaw G, McGaugh J, Rose S pp. 67-86: World Scientific; 1990

Tombaugh GC, Rowe WB, Chow AR, Michael TH, Rose GM (2002) Theta-frequency synaptic potentiation in CA1 in vitro distinguishes cognitively impaired from unimpaired aged Fischer 344 rats. J Neurosci 22:9932–9940.

Tort AB, Kramer MA, Thorn C, Gibson DJ, Kubota Y, Graybiel AM, Kopell NJ (2008) Dynamic cross-frequency couplings of local field potential oscillations in rat striatum and hippocampus during performance of a T-maze task. Proc Natl Acad Sci USA 105:20517-22.

Tort AB, Komorowski RW, Manns JR, Kopell NJ, Eichenbaum H (2009) Theta-gamma coupling increases during the learning of item-context associations. Proc Natl Acad Sci U S A 106:20942-7.

Tort AB, Komorowski R, Eichenbaum H, Kopell N. (2010) Measuring phase-amplitude coupling between neuronal oscillations of different frequencies. J Neurophysiol 104:1195-210.

Tulving, E (1972) Episodic and semantic memory. In Organisation and memory. Edited by Tulving E, Donaldson W, Academic Press

Traub RD, Miles R, Wong RK (1989) Model of the origin of rhythmic population oscillations in the hippocampal slice. Science 243:1319-25.

Ungerleider, L.G., and Mishkin, M. (1982). Two cortical visual systems. In Analysis of Visual Behavior, D.J. Ingle, M.A. Goodale, and R.J.W. Mansfield, eds. (Cambridge, Massachusetts: MIT Press) pp. 549–586

Ugurbil K, Adriany G, Andersen P, Chen W, Garwood M, Gruetter R, Henry PG, Kim SG, Lieu H, Tkac I, Vaughan T, Van De Moortele PF, Yacoub E, Zhu XH (2003) Ultra high field magnetic resonance imaging and spectroscopy. Magn Reson Imaging 21:1263-81

Vanderwolf CH (1969) Hippocampal electrical activity and voluntary movement in the rat. Electroencephalography & Clinical Neurophysiology 26:407-418

van der Meer M, Kurth-Nelson Z, Redish AD (2012) Information processing in decision-making systems. Neuroscientist 18:342-59

Van Dijk H, Schoffelen JM, Oostenveld R, Jensen O (2008) Prestimulus oscillatory activity in the alpha band predicts visual discrimination ability. J Neurosci 28:1816-23

Van Dijk KR, Sabuncu MR, Buckner RL (2012) The influence of head motion of intrinsic functional connectivity. Nueoimage 59:431-8

van Kesteren MT, Fernández G, Norris DG, Hermans EJ (2010) Persistent schema-dependent hippocampal-neocortical connectivity during memory encoding and postencoding rest in humans. Proc Natl Acad Sci USA 107:7550-5.

Vann SD, Aggleton JP (2004) The mammillary bodies: two memory systems in one? Nat Rev Neurosci, 5:35-44.

Vann SD (2010) Re-evaluationg the role of the mammillary bodies in memory. Neuropsychologia, 48:2316-27.

Vann SD, Erichsen JT, O'Mara SM, Aggleton JP (2011) Selective disconnection of the hippocampal formation projections to the mammillary bodies produces only mild deficits on spatial memory tasks: implications for fornix function. Hippocampus, 21:945-57.

Viard A, Doeller CF, Hartley T, Bird CM, Burgess N (2011) Anterior hippocampus and goal-directed spatial decision making. J Neurosci 31:4613-21.

Vincent JL, Patel GH, Fox MD, Snyder AZ, Baker JT, Van Essen DC, Zempel JM, Snyder LH, Corbetta M, Raichle ME (2007) Intrinsic functional architecture in the anaesthetized monkey brain. Nature 447:83-6

Vinogradova OS (2001) Hippocampus as comparator: role of the two input and two output systems of the hippocampus in selection and registration of information. Hippocampus 11:578-98

Voss J. L, Gonsalves B. D, Federmeier K. D, Tranel D, Cohen N. J (2011) Hippocampal brain-network coordination during volitional exploratory behavior enhances learning. Nat Neurosci 14:114–120

Wagner A. D, Schacter D. L, Rotte M, Koutstaal W, Maril A, et al. (1998) Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. Science 281:1188–1191

Wagner AD, Shannon BJ, Kahn I, Buckner RL (2007) Parietal lobe contributions to episodic memory retrieval. Trends Cog Sci 9:445-53

Wang L, Negreira A, LaViolette P, Bakkour A, Sperling RA, Dickerson BC (2010a) Intrinsic interhemispheric hippocampal functional connectivity predicts individual differences in memory performance ability. Hippocampus 20:345-51

Wang L, Laviolette P, O'Keefe K, Putcha D, Bakkour A, Van Dijk KR, Pihlajamaki Dickerson BC, Sperling RA (2010b) Intrinsic connectivity between the hippocampus posteromedial cortex predicts memory performance in cognitively intact older individuals. Neuroimage 51:910-7.

Wang SH, Morris RG (2010) Hippocampal-neocortical interactions in memory formation, consolidation, and reconsolidation. Annu Rev Psychol 61:49-79.

Watanabe T, Niki H (1985) Hippocampal unit activity and delayed response in the monkey. Brain Res, 325:241-254.

Watrous A. J, Fried I, Ekstrom A. D (2011) Behavioral correlates of human hippocampal delta and theta oscillations during navigation. J Neurophysiol, 105: 1747–1755

Watrous AJ, Tandon N, Conner CR, Pieters T, Ekstrom AD (2013) Frequency-specific network connectivity increases underlie accurate spatiotemporal memory retrieval. Nat Neurosci, 16(3):349-65

Watrous AJ, Lee DJ, Izadi A, Gurkoff GG, Shahlaie K, Ekstrom AD (2013) A comparative study of human and rat hippocampal low-frequency oscillations during spatial navigation. Hippocampus, Epub ahead of print

Wegman J, Janzen G (2011) Neural encoding of objects relevant for navigation and resting correlations with navigational ability. J Cogn Neurosci, 23:3841-3854

Weiskopf N, Hutton C, Josephs O, Deichmann, R (2006) Optimal EPI parameters for reduction of susceptibility-induced BOLD sensitivity losses: a whole-brain analysis at 3 T and 1.5 T. Neuroimage, 33:493-504

Wierzynski CM, Lubenov EV, Gu M, Siapas AG (2009) State-dependent spike-timing relationships between hippocampal and prefrontal circuits during sleep. Neuron, 61:587-96

Wig GS, Grafton ST, Demos KE, Wolford GL, Petersen SE, Kelley WM (2008) Medial temporal lobe BOLD activity at rest predicts individual differences in memory ability in healthy young adults. Proc Natl Acad Sci USA, 105:18555-60

Wills T, Lever C, Cacucci F, Burgess N, O'Keefe J (2005) Attractor dynamics in the hippocampal representation of the local environment. Science, 308:873–876

Wilson MA, McNaughton BL (1993) Dynamics of the hippocampal ensemble code for space. Science, 261:1055-8

Winson J (1978) Loss of hippocampal theta rhythm results in spatial memory deficit in the rat. Science, 201:160-163.

Wisse LE, Gerritsen L, Zwanenburg JJ, Kuijf HJ, Luitjen PR, Biessels GJ, Geerlings MI (2012) Subfields of the hippocampal formation at 7 T MRI: in vivo volumetric assessment. Neuroimage, 61:1043-9

Witter M, & Wouterlood F eds. (2002). The Parahippocampal Region: Organization and Role in Cognitive Function (Oxford: Oxford University Press).

Wolbers T, Buchel C (2005) Dissociable retrosplenial and hippocampal contributions to successful formation of survey representations. J Neurosci, 25:3333-40.

Wolbers T, Klatzky RL, Loomis JM, Wutte MG, Giudice NA (2011). Modality-independent coding of spatial layout in the human brain. Curr Biol, 21:984–989

Womelsdorf T, Fries P, Mitra PP, Desimone R (2006) Gamma-band synchronization in visual cortex predicts speed of change detection. Nature, 439:733-6.

Young CK, McNaughton N (2009) Coupling of theta oscillations between anterior and posterior midline cortex and with the hippocampus in freely behaving rats. Cereb Cortex, 19:24-40.

Yu AJ, Dayan P (2005) Uncertainty, neuromodulation, and attention. Neuron, 46:681-92