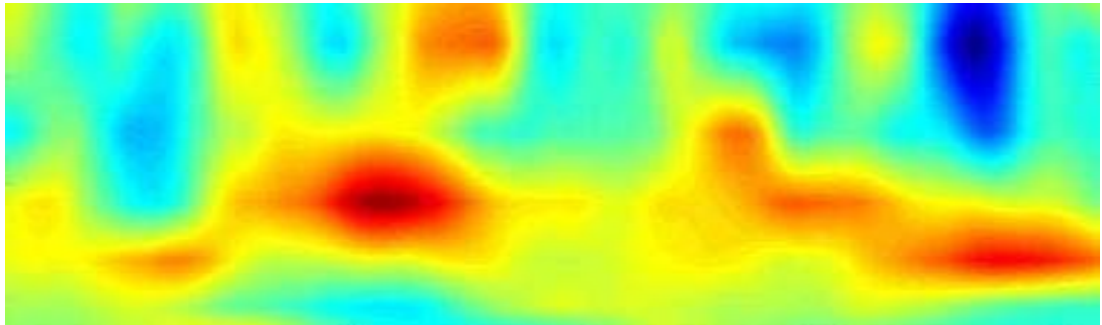# Hippocampus dependent and independent theta-networks of working memory maintenance

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Statement of Originality

I, Nathan Cashdollar, 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. Please note, that the work presented in this thesis on multivariate pattern classifiers in MEG was a collaborative project led by Dr. Lluis Fuentamilla and as such, is presented here as a supplementary discussion (Section 5.5)

Abstract

Working memory is the ability to briefly maintain and manipulate information beyond its transient availability to our senses. This process of short-term stimulus retention has often been proposed to be anatomically distinct from long-term forms of memory. Although it's been well established that the medial temporal lobe (MTL) is critical to long-term declarative memory, recent evidence has suggested that MTL regions, such as the hippocampus, may also be involved in the working memory maintenance of configural visual relationships. I investigate this possibility in a series of experiments using Magnetoencephalography to record the cortical oscillatory activity within the theta frequency band of patients with bilateral hippocampal sclerosis and normal controls. The results demonstrate that working memory maintenance of configural-relational information is supported by a theta synchronous network coupling frontal, temporal and occipital visual areas, and furthermore that this theta synchrony is critically dependent on the integrity of the hippocampus. Alternate forms of working memory maintenance, that do not require the relational binding of visual configurations, engage dissociable theta synchronous networks functioning independently of the hippocampus. In closing, I will explore the interactions between long-term and short-term forms of memory and demonstrate that through these interactions, memory performance can effectively be improved.

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Publications

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Cashdollar, N., Lavie, N., Duzel, E. (2010) Reply to Lee and Baxter: Perceptual deficits cannot explain impaired configural-relational maintenance in bilateral hippocampal injury. Proceedings of the National Academy of Sciences of the United States of America.

Fuentemilla, L., Penny, W. D., Cashdollar, N., Bunzeck, N., Duzel, E. (2010) Theta phase-coupling of working memory content. Current Biology.

Cashdollar, N., Malecki, U., Rugg-Gunn, F. J., Duncan, J. S., Lavie, N., Duzel, E. (2009) Hippocampal dependent and independent theta networks in human working memory. Proceedings of the National Academy of Sciences of the United States of America.

Invited Talks

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Cashdollar, N., Lavie, N., Duzel, E. 'Distraction Improves Memory'. 27th *European Workshop on Cognitive Neuroscience.* Bressanone, Italy. 2010.

Cashdollar, N., Malecki, U., Rugg-Gunn, F. J., Duncan, J. S., Lavie, N., Duzel, E. 'Theta Networks of Active Maintenance'. *Centro Interdipartimentale Mente/Cervello (CIMeC)– University of Trento.* Rovereto, Italy. 2009.

Poster Presentations

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Fuentemilla, L., Penny, D. W., Cashdollar, N., Bunzeck, N., Düzel, E. Theta-coupling of working memory content. *Biology of Cognition*. Chantilly, France, 2008.

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Cashdollar, N., Malecki, U., Rugg-Gunn, F. J., Duncan, J. S., Lavie, N., Duzel, E. Working Memory Configural Delay Maintenance in Magnetoencephalography. *10th International Conference on Cognitive Neuroscience*. Bodrum, Turkey. 2008.

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Germine, L., Cashdollar, N., Duzel, E., Duchaine, B. Within-Category Object Agnosia without Prosopagnosia: A Developmental Case. *15th Cognitive Neuroscience Society*. San Francisco, California. 2008

Germine, L., Cashdollar, N., Duzel, E., Duchaine, B. Dude, where's my car? Developmental object agnosia without prosopagnosia. *Scene Understanding Symposium MIT*. Cambridge, Massachusetts. 2008.

I. Introduction

Traditionally, the ability to retain events over very brief intervals of time (short-term memory) has been thought to be anatomically and functionally distinct from processes necessary for lasting memories (long-term memory). This dichotomy is primarily based on the landmark case-studies of a patient named "H.M." who underwent bilateral temporal lobe resection after which he was unable to create new long-term memories. Furthermore it was believed that in such cases, patients' short-term memory abilities are intact despite their profound deficit in long-term retention. These early seminal studies by Milner and colleagues were pivotal to memory research for identifying the medial temporal lobe, specifically the hippocampus, as the seat of the long-term memory encoding system. Over the past years, recent behavioural and electro-physiological evidence has begun to challenge this classical distinction between long and short-term forms of memory where common functional and anatomical mechanisms may be shared by both. Here, we will briefly introduce the different forms of memory processes, the clinical criteria for the patients studied, and the methodological and theoretical framework which will be the basis of our investigations in subsequent chapters.

1.1. Introduction to Memory

The study of memory has traditionally had the two distinct subdivisions of short-term and long-term memory. Short-term memory is usually considered the retention of information over a very brief interval and was originally considered a retention area for later long-term memory processes. In the past few decades, this rather simplistic view of short-term memory has been extended into a concept considered working memory, which incorporates the manipulation of this information being temporally stored in a workspace as well. This process has been thought to be functionally and neurophysiologically distinct from long-term memory systems. Long-term memory, on the other hand, is considered the process of encoding, storage, and retrieval of information over extended periods of time, often over the course of a lifetime. The nature of information stored during the encoding period will depend on previously learned associations, emotional salience, contextual information, cognitive state, and attention. The resulting memory that is stored for subsequent retrieval can be a conscious representation of experiences and factual knowledge or an unconscious and functional behaviour.

1.2. Long Term Memory

Long term memory can vary greatly from the acquisition of relatively recent information and experiences to the memories that have been consolidated over the course of a lifetime. During the mid-1950s Brenda Milner and colleagues in Montreal ran a series of studies on patients with surgery to alleviate temporal lobe epilepsy. Among these was a patient that seemingly had lost the ability to create any new enduring memories after a bilateral hippocampal resection. This patient has become famous in the memory literature as 'H.M.' and thus began the beginning of medial temporal lobe, specifically the hippocampus, as the seat of long-term memory encoding system (Scoville and Milner, 1957). Continued investigation by Milner's group and many others' work with amnesic patients, such as Larry Squire and Neal Cohen, lead to the separation of distinct systems of declarative and procedural memory within the long term memory process (Squire et al., 1980; Squire et al., 1984). This distinction was based on the evidence at the time that the hippocampus was necessary for conscious memories, hence declarative. Such was the case with

patient H.M.'s impairments evident at the time. While H.M. and other amnesic patients had drastic impairments with declarative encoding, the ability to learn unconscious or more procedural memories were relatively spared. As evidence emerged over time that patients with hippocampal damage could in fact do specific tasks that were considered procedural, this distinction was later revised into Explicit and Implicit memory processes (Schacter and Graf, 1986).

1.2.1. Explicit Memory

Explicit memory is when conscious recollection is required to recall an item, association, or context that has been previously encoded from experience. One of the early pioneers in this field, David Schacter, simply stated it as the "intentional or conscious recollection of prior experiences as assessed in the laboratory by traditional tests of recall or recognition" (Schacter, 1999). The traditional tests of such memory during the time were list recall after considerable delays in humans or the "Delayed non-match to sample test" (DNMST) in monkeys, developed by David Gaffan in Oxford. This task is where an individual sees a stimulus (sample) then later needs to select between two stimuli and decide which stimuli does not match the one seen previously (probe). Early DNMST studies on monkeys showed marked impairments on these tasks after medial temporal lobe lesions when significantly long delays between sample and probe were implemented(Mishkin and Delacour, 1975; Mishkin and Murray, 1994). The early success of these studies in non-human primates were thought to be an animal model of amnesia and thus modelling the memory deficits in patients such as H.M. (Squire and Zola-Morgan, 1991).

Since this earlier work, animal models of explicit memory encoding networks have been researched in great detail. Incoming sensory stimuli from the neocortical areas tend to converge in the rhinal cortices of the medial temporal lobe for an initial integration of sensory information (Suzuki and Amaral, 1994). The perirhinal and parahippocampal regions of the rhinal cortices are the major source of input to the entorhinal cortex and seem to have distinct projections suggesting an anatomical specialization within the encoding process. These entorhinal connections are subdivided where the perirhinal region is dedicated to the rostral two-thirds and the parahippocampus to the caudal two-thirds in the monkey and rat brain (Suzuki and Amaral, 1994; Burwell et al., 1995). The entorhinal cortex then projects to a

unidirectional pathway within the hippocampus called the tri-synaptic circuit. Incoming information via the entorhinal cortex enters the granule cells of the dentate gyrus within the hippocampus and travel through the pyramidal cell layers of CA3 to CA1 terminating at the subiculum. The subiculum of the hippocampus then projects back to the rhinal cortex, which then can project back to the cortical sensory areas, thus completing the circuit (Suzuki and Amaral, 1994; Burwell et al., 1995).

This reciprocal circuit is considered the major pathway of explicit memory encoding, where storage may initially be in the hippocampal areas until sufficient reactivation of this circuit has created a substantial representation in the appropriate cortical areas (Squire & Zola-Morgan, 1991). This differential storage mechanism is in complete accord with the aforementioned studies of epilepsy patients that could not create any new memories after removal of the medial temporal lobe, however, memories encoded prior to surgery were relatively intact. Functional MRI studies have shown increased activity in the hippocampus with successful encoding of explicit memory (Small et al., 2001; Davachi and Wagner, 2002; Reber et al., 2002; Strange et al., 2002; Stark and Okado, 2003) and in retrieval success (Gabrieli et al., 1997; Eldridge et al., 2000; Kirwan and Stark, 2004). Depth electrode recordings used for epileptic seizure foci localization have also shown increased amplitude correlating to successful encoding (Cameron et al., 2001; Fernandez et al., 2002; Fell et al., 2003) and successful retrieval (Paller and McCarthy, 2002). However, this relation to encoding success has not only been attributed to the hippocampus proper, similar results have also been found in the parahippocampal gyrus (Brewer et al., 1998; Wagner et al., 1998; Fernandez et al., 2002; Strange et al., 2002) including the entorhinal and perirhinal cortex (Cameron et al., 2001; Fernandez et al., 2002; Kirwan and Stark, 2004).

Although the involvement of the hippocampus and the rhinal cortex in explicit memory has been well established, the differential contributions of these areas is still speculative. There has been some evidence of anatomical specificity within this network where increased BOLD signal within CA2, CA3, and the dentate gyrus of the hippocampus and the parahippocampus were correlated with successful encoding while successful retrieval was related to activation in the subiculum (Pihlajamaki et al., 2003; Zeineh et al., 2003). While others have found no significant differences of retrieval and encoding within hippocampus, perirhinal, and parahippocampal neocortex (Stark and Okado, 2003).

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The various hypotheses of this anatomical specialization within explicit memory processing usually tend to adhere to either a qualitative or quantitative distinction of function. Qualitatively, the hippocampus is involved with explicit memories of associations, multi-item, spatial, episodic, and recollection; while the parahippocampal areas tend to process more automatic, non-effortful, single item, familiar, and recent information (Brown and Aggleton, 2001). Quantitatively, the medial temporal lobe memory network functions more broadly in explicit memory where the individual sensory units from the cortex are integrated into a comprehensive experience or representation by the rhinal areas, which is then stored initially in the hippocampus and later in their corresponding cortical areas. Whereas all these structures within the medial temporal lobe make differential contributions of association and conjunctive processing (Squire and Zola-Morgan 1991).

1.2.2. Semantic and Episodic Memory

The conscious recollection of an experience that occurs only once and within a particular context and moment in time is qualitatively very different than the knowledge of facts that are gradually accumulated and are usually contextually non-specific. This descriptive distinction of explicit memory was originally proposed in the 1970s (Tulving, 1977). Tulving suggested that episodic memory is the encoding of personal episodes or experiences requiring conscious recollection of a temporal and spatial context in which the moment occurred. Tulving considered this a binding of the event (What), place (Where), and a time (When) thus creating a coherent experience (Tulving, 1977). While semantic memory, in comparison, is considered the "culturally shared general knowledge about the world" of specific facts where the conscious encoding of context is unnecessary (Graham et al., 2000).

Emerging evidence from studies by Mort Mishkin and Vargha-Khadem on school children with focal hippocampal damage later supported such a neurological basis for this distinction. These children tended to have relatively intact semantic memory encoding abilities, however their episodic memories of the personal experiences were severely impaired (Vargha-Khadem et al., 1997; Mishkin et al., 1998). Based on previous detailed neuroanatomical studies of the hippocampal system in monkeys (Suzuki and Amaral, 1994), it could be proposed that a selective lesion to the hippocampus could disrupt encoding processes specific to this area (i.e.

episodic), while lesions to the surrounding parahippocampal regions projecting to the hippocampus via the entorhinal cortex would disrupt the entire explicit memory network (Mishkin et al., 1998). The previous studies of medial temporal lobe damage in temporal lobe epilepsy patients were probably more diffuse involving parahippocampal regions as well, which could explain their loss of both episodic and semantic encoding. In the case of H.M., it was later confirmed by MRI that his medial temporal lobe removal included entorhinal cortex and perirhinal cortex, as well at the rostral portion of the hippocampus (Corkin et al., 1997).

Accumulating evidence dissociating episodic and semantic memory as distinct systems has lead to revisions of this model where episodic memory is a subsystem of semantic memory (Tulving and Markowitsch, 1997). Under this assumption, the perceptual stimulus initially is processed by the semantic system which is then fed into the hippocampus to be blended into a meaningful episodic memory if appropriate. Some recent work with patients suffering from Semantic Dementia has even suggested that episodic and semantic encoding may be reciprocal systems that will give a relative amount of memory encoding depending on the nature of the explicit memory to be encoded (Graham et al., 2000). However, other researchers such as Larry Squire and Stuart Zola still feel the hippocampus and the parahippocampal cortex constitute a single explicit memory system that incorporates both semantic and episodic memory.

1.2.3. Recognition Memory: Familiarity and Recollection

Behavioural experiments during the 1970s and 1980s on episodic recognition memory began to uncover some qualitative differences concerning target recognition when experimenting with the confidence ratings of individuals' responses (Jacoby and Dallas, 1981). This led to a psychological distinction between the process of recognizing a stimulus, such as a picture, or a word; on the basis of the retrieval of specific contextual details and the process of recognizing an item based on it's perceived memory strength, in the absence of any specific details about the stimulus or context (Jacoby and Dallas, 1981). The traditional test for this dissociation is called the 'Remember Know' paradigm designed by Tulving (Tulving et al., 1988). During these tests an individual can 'know' a stimulus, hence can be familiar with a target stimuli, however, have no recollection of when or where it previously

occurred. Alternatively, the individual can recollect the situational context in which the stimulus was presented and thus 'remember' it (Gardiner, 1988; Tulving et al., 1988). Both of these forms of recognition memory satisfy the conscious prerequisite necessary for explicit memory, however, the recollection of the source or association in which it occurred is an important distinction between these two abilities. Actively remembering the temporal and surrounding environment (where & when) requires the individual to undergo a "mental time travel" to re-experience the contextual details of the situation (Diana et al., 2007).

Later work by Andrew Yonelinas during the 1990's, incorporated some important aspects of signal detection theory into characterizing the dissociation of familiarity and recollection processing. His group plotted the behavioural results of recognition memory tests into two probability functions called Receiver Operating Characteristic (ROC) curves. Where one axis would be the correctly identified stimuli "hits" and the other is the incorrectly identified stimuli "false alarms" for both familiarity and recollection judgments (Yonelinas, 2001). The resulting ROC curves displayed a symmetrical distribution for familiarity ratings, however the distribution of recollection would shift asymmetrically depending on the relative cost/benefit assessment of their responses. Yonelinas proposed this to be a dual processing mechanism where familiarity is an equal-variance signal-detection mechanism while recollection is a threshold process (Yonelinas, 2001; Yonelinas and Parks, 2007). Complementary results were found in rats where the recollection ROC distributions of hippocampal lesioned rats tended to be symmetrical when compared to before surgery despite the cost/benefit ratio for rewards (Fortin et al., 2004). Suggesting that the hippocampus may be necessary for the recollection component of recognition memory within the duel processing model (this notion will be further discussed in Chapter 7).

Since Yonelina's original proposal, a number of other dual processing and binding models have emerged in the literature, however, the neuroanatomical dissociation of familiarity and recollection has gained considerable evidence in structural MRI (Yonelinas and Parks, 2007) functional MRI (Duarte et al., 2004; Ranganath and D'Esposito, 2005) and event-related potential recordings with EEG (Mackenzie and Donaldson, 2007; Rugg and Curran, 2007). The general agreement is that recollection encoding and retrieval tends to be correlated with increased activity in the hippocampus and the post parahippocampal gyrus. In comparison,

encoding of familiar items correlates with perirhinal cortex activity and retrieval with decreased activity in this area (Diana et al., 2007). Imaging studies and knowledge of the cortical inputs from these regions suggests that the perirhinal cortex receives more information concerning item features while the post parahippocampal gyrus is more concerned with integrative and contextual information that becomes blended into recollective information in the hippocampus.

1.2.4. Implicit Memory

The other major branch of long-term memory is non-declarative or what is now commonly known as 'implicit memory'. Implicit memory refers to memory in which previous experiences from one's life will affect the performance of a task without conscious awareness or intentional recollection of those experiences (Graf and Schacter, 1985). In fact, the major delineation of implicit from explicit memory long-term memory is the unconscious processing that leads to the changes in performance and how this processing is thought to be completely divorced from the medial temporal lobe structures critical for explicit memory (Brooks and Baddeley, 1976; Graf and Schacter, 1985).

Undoubtedly the most common example of implicit processes is that of procedural memory, where during one's day-to-day life, an individual doesn't have to re-learn how to tie their shoes in the morning or operate the gear-shift in their car. These procedural memories are unconsciously remembered in their habitual form. Other less obvious forms of implicit memory are Pavlov's infamous classical conditioning, non-associative 'reflexive' learning, and priming. An exhaustive discussion of implicit memory and it's various sub-divisions is beyond the scope of this current work and will not be a focus of the research to be presented here - *for review and history see* (Schacter, 1987). However, it is important to note, that implicit memory learning has been shown to be intact in patients with medial temporal lobe damage (Jacoby and Dallas, 1981; Schacter et al., 1982; Graf and Schacter, 1985).

1.3. Short-term working Memory

Short term memory is usually considered the retention of discrete information over very brief intervals of just a few seconds. In the past few decades, this rather simplistic view of short term memory has been extended into a concept considered working memory, which incorporates the manipulation of this information being temporally stored in a workspace (Baddeley and Hitch, 1974). This ability to actively maintain an otherwise transient visual stimulus within a workspace for short delayed recall, manipulation, or association has often been referred to as the "Blackboard of the mind" (Goldman-Rakic, 1996) or the "Visio-Spatial Sketch Pad" (Baddeley, 1998). The concept of working memory proposes a transient capacity limited system which supports human thought processes (Baddeley, 2003) and has been shown to be strongly predictive of intelligence and reasoning abilities (Fukuda and Vogel, 2009). An in depth discussion of working memory capacity limits (i.e. working memory load) and the neuroanatomical correlates of maintaining increased demands of discrete information will be discussed in Chapter 3.

The predominate cognitive theory of working memory was proposed in the mid-1970's by Baddeley and Hitch (1974), where two short-term storage systems interact with a central processing system known as the 'central executive'. Probably the most studied component of the two short-term storage systems is the 'phonological loop' where memory traces of articulatory rehearsal allow the brief maintenance of verbalized material. The most common example, is when you are attempting to remember a phone number and you sub-vocally rehearse this number in your mind until dialling. This notion has been supported behaviourally by experiments showing decreased performance remembering strings of words or letters when internal articulatory rehearsal is suppressed (Murray and Roberts, 1968) and complimentary neuropsychological evidence of lesion patients with phonological short-term memory impairments in the absence of language deficits (Baddeley, 1984). The other storage component has been termed the 'Visio-Spatial Sketch Pad', where like it's verbal equivalent, visual information is actively replayed during short-term working memory maintenance (visual working memory will be comprehensively discussed though-out subsequent chapters). This three-component model was later revised to include a module known as the 'episodic buffer' that allows the interaction of the aforementioned working memory processes with

episodic long-term memory representations (Baddeley and Hitch, 2000). This notion of functional interactions between long-term memory processes and short-term working memory maintenance will be explored in Chapters 6 and 7 - *for review of the multi-component model of working memory see* (Baddeley, 2003).

Continued investigations by Milner's group (1972) and others (Drachman and Arbit, 1966; Wickelgren, 1968) found that amnesic patients with medial temporal lobe damage displayed intact performance on tests where the retention of material was only for a few seconds. Since these early studies, short-term memory has been consistently thought of as an independent memory system that is spared in patients with medial temporal lobe damage (Atkinson and Shiffrin, 1971; Milner, 1972; Shrager et al., 2008).

Soon after the pivot studies released by Milner, it was found that single cell recordings of non-human primates within regions of the pre-frontal cortex displayed persistent neural firing during the active maintenance of visual information over working memory delays (Fuster and Alexander, 1971). Since this discovery, activity in the prefrontal cortex during delay periods of visual working memory tasks have been well established in animals (Funahashi et al., 1989; Nacher et al., 2006) and fMRI studies of humans (D'Esposito et al., 2000; Haxby et al., 2000; Postle et al., 2000). The short-term maintenance of information is now thought to be made possible by the functional engagement of cortical regions involving the prefrontal and the parietal cortices (Cohen et al., 1997; Courtney et al., 1997; Baddeley, 1998; Sarnthein et al., 1998; D'Esposito et al., 2000; Haxby et al., 2000; Postle et al., 2000; von and Sarnthein, 2000; Deiber et al., 2007).

Together, this evidence has led to the notion of two functionally and neurophysiologically distinct memory systems. The first, is declarative long term memory processes that are dependent upon medial temporal lobe structures (hippocampus, perirhinal, entorhinal, and parahippocampal cortices) for the encoding, storage, and retrieval of information over extended periods of time, often over the course of a lifetime (Squire and Zola-Morgan, 1991). The second, is a distinct alternate short-term memory system allowing information from transient events to persist in the brain as active representations. This working memory system thus enables goal-directed behaviours such as decision making and learning to utilize and manipulate information beyond its transient sensory availability (Baddeley, 1998). However, over the past years, recent behavioural and electro-physiological

evidence has begun to challenge this classical distinction between long and short-term forms of memory where functional and anatomical commonalities may be shared by both.

1.4. Questioning distinctions between short- and long-term memory

Intriguing behavioural evidence has emerged over the past decade that the hippocampus may be involved in the short-term maintenance of the relational binding between objects (Hannula et al., 2006; Olson et al., 2006a; Hannula and Ranganath, 2008) and the topographical representation of this visual information (Hartley et al., 2007). Recently it has been demonstrated that amnesic patients with selective hippocampal atrophy display working memory impairments for the spatial configuration of objects over short delay periods (Hannula et al., 2006; Olson et al., 2006a). For instance, after a brief presentation of a natural scene, these patients are unable to keep in mind the configural association between multiple objects within that scene (Hannula et al., 2006; Hartley et al., 2007). Strikingly, this deficit is evident even at very short delays of just a few seconds of working memory maintenance.

These results suggest that the medial temporal lobe, which has traditionally been associated with long-term memory (Squire et al., 1980), may also be critical to the maintenance of associative visual information of spatial configurations in working memory. In accordance with this view, a number of imaging studies have shown increased activity in the hippocampus and surrounding medial temporal lobe areas during the delay period of working memory using fMRI (Cabeza et al., 2002; Monk et al., 2002) and using MEG (Campo et al., 2005). Amnesic patients have recently been found to be impaired on other forms of relational visual memory (associative and sequence) and not strictly spatial configurative relations, while their ability to retain items non-associatively is relatively intact (Konkel et al., 2008). Therefore, deficits in the visuo-spatial components of these tasks may be a product of a more generalized impairment in relational binding due to hippocampal damage. Previous dissociations between long and short-term memory processes need to be re-evaluated in order to incorporate these recent findings - *for review see* (Ranganath and Blumenfeld, 2005) and will be the focus of the research presented in subsequent chapters.

1.5. Introduction to Epilepsy

Epilepsy has been defined as the chronic occurrence of unprovoked seizures caused by uncontrolled discharges of cerebral neurons. Depending on the region of the brain where seizures occur and the subsequent spread of the epileptic discharge, the resulting clinical manifestation of individuals suffering from epilepsy can greatly vary. Because of this variability of symptom presentation, epilepsy can be difficult to diagnose with specificity in the absence of extensive diagnostic testing and is often initially confused with other conditions that can cause seizures, such as diabetes, heart disease, or depression. Epilepsy is one of the most common neurological diseases in the world, affecting approximately 50 million people world-wide and over 450,000 people in the United Kingdom alone (Everitt and Sander, 1998).

Approximately 60-70% of focal seizures originate in the temporal lobe, the majority of which are localized in the hippocampus. As previously discussed, the hippocampus and surrounding medial temporal lobe, are critical to many forms of memory and consequently individuals suffering from epilepsy seek help for memory problems more than any other kind of impairment. In hospital-based MRI studies, hippocampal sclerosis (i.e. reduced volume of the hippocampus proper) was identified in 25-30% patients with focal epilepsy (Everitt and Sander, 1998; Wieshmann, 2003), however, short-term memory has often been reported to be intact in epilepsy patients with medial temporal lobe lesions (Drachman and Arbit, 1966; Milner, 1972). The investigation of short-term memory deficits in epilepsy patients with bilateral hippocampal sclerosis and the dependence of certain forms of working memory maintenance on hippocampal integrity will be the focus of subsequent chapters (see Chapters 4, 5, & 7).

1.5.1. Seizure classification

Early systems of seizure classification lacked the specificity to differentiate between seizure type and syndrome. For instance, the term 'grand mal' was often used to describe any form of tonic-clonic seizure (see term definitions below) and likewise, the term 'petit mal' was used to describe any minor form of seizure which could encompass both absences and complex partial seizures. This diagnostic

criteria was later revised in 1981 by the Commission on Classification and Terminology of the International League Against Epilepsy (ICES) that would differentiate seizure types by clinical manifestation and electrophysiological recordings. Although the ICES classification system has gained acceptance as the predominate diagnostic criteria in contemporary clinical assessments, some are critical that this system still lacks the specificity needed for a complete characterization of epileptic activity (Manford et al., 1992; Luders et al., 1993).

The ICES system is first organized according to whether the source of the seizure is localized in the brain (partial – focal onset) or the source is distributed across cortical regions (generalized). Partial seizures are then further sub-divided if consciousness is determined to be affected (complex) or not (simple) during the epileptic event. All generalized seizures involve some degree of affected consciousness and are also further sub-divided based on their outward behavioural and motor characteristics (absence, myoclonic, clonic, tonic, tonic-clonic, and atonic). – see **Table 1.1**

International Classification of Epileptic Seizures

I. Partial seizures

    A. Simple partial seizures

        1. With motor symptoms

            a). Focal motor without march

            b). Focal motor with march (Jacksonian)

            c). Versive

            d). Postural

            e). Phonatory

        2. With somatosensory or special-sensory symptoms

            a). Somatosensory

            b). Visual

            c). Auditory

            d). Olfactory

            e). Gustatory

            f). Vertiginous

3. With autonomic symptoms or signs

4. With psychic symptoms

    a). Dysphasia

    b). Dysmnesic

    c). Cognitive

    d). Affective

    e). Illusions

    f). Structured hallucinations

B. Complex partial seizures

1. Simple partial seizures at onset, followed by impairment of consciousness

    a). With simple partial features

    b. With automatisms

2. With impairment of consciousness at onset

    a). With impairment of consciousness only

    b). With automatisms

C. Partial seizures evolving to secondarily generalized seizures

1. Simple partial seizures evolving to generalized seizures

2. Complex partial seizures evolving to generalized seizures

3. Simple partial seizures evolving to complex partial seizures evolving to generalized seizures

II. Generalized seizures

A. Absence seizures

1. Typical absence seizures

    a). Impairment of consciousness only

    b). With mild clonic components

    c). With atonic components

    d). With tonic components

    e). With automatisms

    f). With autonomic components

2. Atypical absence seizures

B. Myoclonic seizures

C. Clonic seizures

D. Tonic seizures

E. Tonic-clonic seizures

F. Atonic seizures

Table 1.1. International Classification of Epileptic Seizure (ICES) created by the International League Against Epilepsy in 1981.

1.5.2. Syndrome classification

The classification of epileptic seizures describes the symptomology of epileptic discharges, however, often lacks the aetiological specificity needed for prognostic evaluations of patients suffering from this condition. In 1985, the International Classification of the Epilepsies and Epileptic Syndromes (ICEES) was developed for classification of the individual syndromes of epilepsy and it's slightly revised version (ICEES 1989b) is now considered the standard diagnostic criteria for clinical evaluations. Similar to the ICES, this system is primarily divided into cases where the seizure focus is localized or generalized (also with divisions for 'undetermined' and 'special' syndromes), with these branches further sub-divided into idiopathic and symptomatic characterizations (**Table 2.2**). Localized (focal) epilepsy syndromes are also then further characterized according to their anatomical localization, such as temporal lobe epilepsy. It is important to note, that in the light of recent technological advances in neuroimaging and genetics, the ICEES system is being reappraised by the International League Against Epilepsy to incorporate these techniques in the diagnostic criteria of epilepsy syndromes.

The International Classification of the Epilepsies and Epileptic Syndromes

I. Localization-related epilepsies and syndromes
    A. Idiopathic (with age-related onset)
        1. Benign childhood epilepsy with centrotemporal spike
        2. Childhood epilepsy with occipital paroxysms
        3. Primary reading epilepsy
    B. Symptomatic
        1. Chronic progressive epilepsia partialis continua of childhood

2. Syndromes characterized by seizures with specific modes of precipitation.

3. Temporal, frontal, parietal and occipital lobe epilepsies

C. Cryptogenic

1. Temporal, frontal, parietal and occipital lobe epilepsies

II. Generalized epilepsies and syndromes

A. Idiopathic (with age-related onset)

1. Benign neonatal familial convulsions

2. Benign neonatal convulsions

3. Benign myoclonic epilepsy in infancy

4. Childhood absence epilepsy (pyknolepsy) / Juvenile absence epilepsy

5. Juvenile myoclonic epilepsy

6. Epilepsy with GTCS seizures on awakening

7. Other generalized idiopathic epilepsies not defined above

8. Epilepsies with seizures precipitated by specific modes of activation.

B. Cryptogenic or symptomatic

1. West syndrome (infantile spasms, Blitz-Nick-Salaam Krampfe)

2. Lennox-Gastaut syndrome

3. Epilepsy with myoclonic-astatic seizures

4. Epilepsy with myoclonic absences

C. Symptomatic

1. Non-specific aetiology

2. Early myoclonic encephalopathy

3. Early infantile epileptic encephalopathy with suppression burst

4. Other symptomatic generalized epilepsies not defined above

5. Epilepsies due to specific neurological diseases

III. Epilepsies and syndromes undetermined whether focal or generalized

A. With both generalized and focal seizures

1. Neonatal seizures

2. Severe myoclonic epilepsy in infancy

3. Epilepsy with continuous spike-waves during slow wave sleep

4. Acquired epileptic aphasia (Landau-Kleffner-syndrome)

5. Other undetermined epilepsies not defined above

B. Without unequivocal generalized or focal features.

IV. Special syndromes

    A. Situation-related seizures

        1. Febrile convulsions

        2. Isolated seizures or isolated status epilepticus

        3. Seizures occurring only when there is an acute metabolic or toxic event

Table 1.2. The International Classification of the Epilepsies and Epileptic Syndromes (ICEES) – Version: 1989b.

1.5.3. Hippocampal epilepsy

The pathophysiology of seizure generation and propagation in epilepsy is poorly understood, however, influential theoretical models suggest a possible deregulation of the normal balance between synchronous excitatory and inhibitory synaptic firing can give rise to epileptogenic spike-wave discharges (Jefferys and Traub, 1998; Traub et al., 1998). Furthermore, the hippocampus has been proposed to be especially prone to such a synaptic hyper-synchronicity due to the complex matrix of multiple excitatory glutamatergic feed-back loops within and between the many sub-regions of the hippocampus (Miles and Wong, 1986; Wong et al., 1986).

For illustration purposes, a single pyramidal cell in the CA3 region of the rat hippocampus is thought to connect with 25,000 – 50,000 synapses within the same hippocampus and the CA3 region as a whole is estimated to have 5-10 billion synaptic connections within each hemisphere (Tamamaki et al., 1988). A minor de-synchronization of this dense network due to microdysgensis (Meencke and Janz, 1984), lesions (Ferrer et al., 1992), or any form of tissue abnormality (Jefferys and Traub, 1998) could then lead to the propagation of this electrical surge throughout the inter-connected hippocampal cytoarchitecture, resulting in an exponentially larger epileptic discharge (in physics this is analogous to what is known as a 'bifurcation point' in non-linear dynamics).

Indeed the majority of focal seizures originate from the medial temporal lobe, specifically the hippocampus (Everitt and Sander, 1998); and hippocampal damage is the most common pathology found in chronic temporal lobe epilepsy (Babb et al., 1987).

Hippocampal sclerosis is found in approximately 60% of temporal lobes removed for the treatment of epilepsy, and is associated with 60-70% chance of the patient becoming seizure free following resection (Everitt and Sander, 1998).

Volumetric reductions in the case of hippocampal sclerosis can often be determined from anatomical images of T1-weighted magnetic resonance imaging (MRI). Additional MRI features characteristic of hippocampal sclerosis are increased signal intensity within the hippocampus on T2-weighted images (Berkovic et al., 1991). Individually these two MRI measures may be indicative of various other pathologies, however, the combination of T1 volume loss and T2 abnormal signal intensity is thought to be highly specific for hippocampal sclerosis (see Chapter 4).

As discussed earlier, the medial temporal lobe and the hippocampus are vital to the long-term memory system (Squire and Zola-Morgan, 1991) and it is evident that patients with temporal lobe epilepsy suffer from severe deficits in the encoding, storage, and retrieval of newly established information. Exhaustive studies have highlighted the characteristic long-term memory impairments in these patients and as such, have served as an excellent model by which to examine the neuroanatomical correlates of human memory functioning - *for review see* (Leritz et al., 2006). In the following chapters, we intend to expand these investigations of memory function in temporal lobe epilepsy patients with selective hippocampal damage in order to characterize specific short-term working memory processes that are dependent upon hippocampal integrity.

1.6. Introduction to Oscillations

The ionic conductance responsible for the excitability of single neurons can result in dynamic electrical resonance and oscillatory activity (Llinas, 1988; Hutcheon and Yarom, 2000). The architecture of neural networks and the relative speed of connectivity between these cells (due to axon conduction and synaptic delays in signalling), creates emergent oscillations that resonate at differing frequencies. The self-organizing nature of neural variability between these cells is thought to give rise to an internal homeostatic rhythm within the brain that becomes perturbed from incoming sensory stimuli (Friston, 2000; Buzsaki et al., 2002; Buzsaki and Draguhn, 2004). As a result, dynamic shifts in neural firing reverberate

through the brain's neural architecture providing a transient accommodation in oscillatory activity. It has therefore, been suggested that the precise timing of this activity within an assembly can be a means of conveying information (Buzsaki and Draguhn, 2004). The spatial-temporal organization of interactions between neurons, in the form of oscillatory rhythms, gives rise to functional connectivity and thereby creating a neural assembly, or network, in which transient information can persist.

The relative lengths of these oscillatory cycles limit the synaptic transmission of distant neural connectivity between cortical structures (Buzsaki and Draguhn, 2004). Therefore, oscillatory rhythms within the lower frequency spectrum are thought to coordinate the relative firing of distant neural assemblies, while fast oscillations (i.e. Gamma-Band) favour local interactions. These rhythms specifically within the theta frequency band (4-12 Hz) have been proposed to be a general clocking mechanism in which to integrate the functional cooperation of distant assemblies into a coherent network (Sarnthein et al., 1998; Jones and Wilson, 2005). Theta band oscillations have been shown to functionally enhance the interactions of local and distant neural networks (Jones and Wilson, 2005) and has been implicated in processes such as synaptic plasticity (Arai and Lynch, 1992; Huerta and Lisman, 1995), spatial navigation (Kahana et al., 1999; Caplan et al., 2001; Caplan et al., 2003), memory encoding (Huxter et al., 2003), recollection (Guderian and Duzel, 2005), mental imagery (Sarnthein et al., 1998), and delay maintenance (Raghavachari et al., 2001; Lee et al., 2005b; Raghavachari et al., 2006). The relationship of theta band oscillations supporting working memory maintenance will be discussed in greater detail in the following chapter.

1.7. Introduction to Magnetoencephalography

Magnetoencephalography (MEG) is a relatively recent technique developed for detecting oscillatory brain activity non-invasively from the surface of the scalp in humans. Voltage changes during synaptic transmission within the brain are accompanied by corresponding magnetic field changes. MEG can detect this weak magnetic fields (on the order of pico-tesla) generated by neural activity via a superconducting quantum interference device (SQUID) that amplifies magnetic changes recorded from an array of sensors situated around the scalp. In contrast to the commonly used technique of electroencephalography (EEG), the MEG signal is

thought to reflect intracellular currents mainly from the cortical fissures of the brain making it a more suitable technique for recording hippocampal activity. Also, MEG is thought to have a more homogeneous representation of the electromagnetic changes in the brain because magnetic fields are not as susceptible to signal distortion from the skull as is the case in electrical field recordings of EEG.

Research Aims

In a series of working memory experiments using MEG we will investigate cortical synchronization within the theta band during the active working memory maintenance of visual information in normal controls and epilepsy patients with bilateral hippocampal sclerosis. Through a convergence of evidence, we hope to elucidate a rhythmic neural mechanism in which the hippocampus supports active representations of visual configurations relationships by coordinating the functional synchronization of different cortical regions, which is behaviourally and functionally dissociable from non-configural-relational forms of maintenance. We will determine if actively maintaining the configural-relational aspects of a visual scene is associated with theta oscillatory coupling of temporal and occipital visual areas (Chapter 2) and furthermore, if this theta-network is critically dependent on the integrity of the hippocampus (Chapter 5). Behaviourally, we will investigate if configural-relational forms of working memory critically depend on hippocampal integrity and if these deficits are due to difficulties in perceptual integration (Chapter 4) or quantitative increases in working memory maintenance demands (Chapter 7). Furthermore, we intend to dissociate this network from non-configural-relational forms of working memory maintenance functionally via theta-network connectivity (Chapter 2 & 3) and behaviourally (Chapters 4, 5, 6 & 7). Chapters 6 and 7 will explore interactions between long-term memory encoding and short-term working memory maintenance. In light of these interactions, we will demonstrate that under circumstances in which working memory maintenance processes are faulty, disruption of maintenance may lead to improved hippocampal independent recognition performance (Chapter 7). In closing we hope to have characterized dissociable theta-networks of hippocampal-dependant and hippocampal-independent forms of working memory maintenance, and thereby challenge classical distinctions between short-term and long-term memory.

II. Differential Networks of Active Maintenance

Rhythmic patterns of neural firing are ubiquitous throughout the cortex. This internal homeostatic rhythm can become externally modified by stimuli arriving from the senses. Maintaining a representation of this external reality is thought to be accomplished by the continual internal adjustments of these self-generated patterns. Here, we aim to utilize this framework to investigate how the brain's rhythmic oscillations of neural activity can synchronize to create functional networks of stimulus persistence in working memory. Recent evidence from single unit recordings in rodents and lesion studies in humans have suggested that medial temporal lobe theta band coherence may reflect a functional network supporting maintenance of spatial associations over retention periods. This chapter will investigate the differential cortical synchronization (theta phase-coupling) during the active maintenance of the configural relationships of visual information compared to non-configural-relational working memory maintenance.

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2.1. Introduction

Theta frequency oscillations have been well established in spatial navigation and hippocampal encoding of location within a place field in rats(O'Keefe and Conway, 1978; O'Keefe, 1993; Huxter et al., 2003), however, a recent study using simultaneous tetrode recordings in rodents has demonstrated significant phase locking of CA1 hippocampal regions to medial prefrontal cortex (mPFC) phasic firing during T-maze navigation (Jones and Wilson, 2005). The functional coupling of these structures was significantly enhanced when the active maintenance of goal and target location were needed to be kept in working memory in order to successfully complete task demands (Jones and Wilson, 2005). The CA1-mPFC entrainment was specific to a 4 – 12 Hz cycle and strengthens the organizational role of theta rhythms during the delay periods of spatial working memory (Jones and Wilson, 2005).

One hallmark of active maintenance is the persistent neural firing in the PFC during the delay periods of visual working memory tasks (Funahashi et al., 1989; Constantinidis et al., 2001; Miller and Cohen, 2001; Nacher et al., 2006). This delay activity has been thought to an important mechanism in which behavioural goals can be kept online (Rainer et al., 1998; Asaad et al., 2000; Miller and Cohen, 2001) and modified according to changing task demands and contingencies (Asaad et al., 1998). The neuroanatomy of this network shows that the hippocampus projects uni-directionally to the mPFC regions suggesting that CA1 firing is primarily driving the synchronization of these areas (Swanson, 1981; Jay et al., 1989).

Similarly, theta frequency band elevations have been implicated in occipital visual cortex during working memory (Raghavachari et al., 2001), as well as, synchronization of these areas with the PFC during delay maintenance (Sarnthein et al., 1998). Local field potential measurements in area V4 of the extrastriate cortex of monkeys during visual delay maintenance have shown preferential single unit neural firing at a particular phase of the theta rhythm (Lee et al., 2005b). This entrainment of single unit activity to a preferred phase angle of the theta cycle was modulated by stimulus selectivity during maintenance and was independent of generalized increases in firing (Lee et al., 2005b). Not only does this provide evidence for the importance of theta organization from single neurons to large-scale cortical synchronization during working memory delays, but suggests that this stimulus-

selective theta activity may be a form of information representation during maintenance. A similar pattern of preferential firing during particular phase angles of theta have been found in the hippocampal pyramidal neurons of rodents during navigation (O'Keefe, 1993; Buzsaki et al., 2002).

As described in Chapter 1, it been well established that the medial temporal lobe is critical to long-term declarative memory (Cohen and Squire, 1980), however, recent evidence in humans has suggested that the hippocampus may be involved in the short-term retention of the relational binding between objects (Olson et al., 2006a; Olson et al., 2006b; Hannula and Ranganath, 2008) and their topographical representation (Hartley et al., 2007). For instance, amnesic patients with selective hippocampal atrophy have displayed working memory impairments over short delays for the spatial configuration of objects (Hannula et al., 2006). Overall, suggesting that the hippocampus may coordinate the recruitment of the ventral visual stream (via theta band coupling) in order to maintain the associative information of configural stimuli over delays.

Experiment 1. Configural-relational working memory maintenance in normal controls

2.1. Aims 1

Using MEG recordings in healthy participants, we intend to establish that the maintenance of configural-relational and non-configural-relational forms of visual information (*see methods section for term definitions*) can be differentially characterized by induced phase-coupling within the theta band. We hypothesize that the active maintenance of configural-relational information will enhance theta connectivity in sensor groups along the ventral visual processing areas and the medial temporal lobe. Alternatively, non-configural-relational forms of working memory maintenance should engage a theta network involving frontal and parietal sensors, comparable to previous reports (Haxby et al., 2000; Postle et al., 2000; Deiber et al., 2007). Since active maintenance should tend to have a loose temporal relationship (i.e. not time-locked to a stimulus event) induced oscillatory activity was investigated in order to yield information on the dynamics of cell assemblies during delays in working memory tasks (Deiber et al; 2007). Furthermore, we chose to

investigate oscillatory activity specifically within the theta band because of its intrinsic properties of integrating the functional cooperation of distant assemblies into a coherent network (Jones and Wilson, 2005, Sarnthein et al., 1998).

2.3. Study Design 1

2.3.1 Participants.

Eight right-handed healthy subjects (5 male / 3 female mean age 21.6; SD ± 3.2 years) participated in the experiment. All participants were recruited from the University College of London's Psychology departmental subject pool and were determined to have no extraneous neurological or psychological disorders that would confound our results. In addition, all subjects displayed normal or corrected to normal visual acuity. All participants gave written informed consent to participate and the study was approved by the guidelines of the ethics committee of the University of London Research Ethics Committee for human-based research. All participants were compensated at a rate of £6 per hour for the entirety of the study, which averaged two hours to complete.

2.3.2. Stimuli and Task.

The stimuli used in this experiment were photographs of 260 indoor and 260 outdoor scenes. All pictures were grey scaled and normalized to a mean grey value of 127 and an SD of 75, set at 300x300 pixels, and shown upon a grey background (127 value). The experiment consisted of three conditions: a 'non-configural-relational' delayed-match-to-sample (DMS) condition, a 'configural-relational' DMS condition, and a 'control' condition. In all three conditions, the trial structure and stimulus-timing were identical (**Figure 1.1**). After a 2 sec inter-trial-interval, an indoor or an outdoor scene was presented for 3 sec. This was followed by a blank screen with a fixation cross for 5 sec and then by two test stimuli for 4.5 seconds.

In all three conditions, participants were required to make a speeded indoor/outdoor discrimination for the sample image indicated by button press using the index or middle finger of the right hand. In the DMS conditions, the two test images after the delay interval were used to probe memory for the sample. In the

non-configural-relational DMS, one of the probes was an exact repetition of the sample and the other depicted an entirely difference novel scene of the same category (indoor or outdoor) as the sample. Participants' were instructed to maintain the sample image in their memory in order to be able to correctly identify the matching sample. The location of the matching probe and the non-matching foil (left vs. right presentation) were counterbalanced across trials.

In the configural-relational trial condition stimuli were manipulated in a relatively similar fashion as reported by (Ryan et al., 2000; Ryan and Cohen, 2004). Manipulated versions of the scenes involved changes in the relations among some elements of the scenes. The types of manipulations were (a) addition or deletion of a new object or (b) a spatial shifting of an object within a scene. Manipulation type (a) was used in 56% of the trials and type (b) was used in 44% of the trials in the configural-relational DMS conditions. Thus during sample scene presentation in the configural-relational condition, participants were required to encode the individual objects (e.g. a tree, a bench) as well as object-object (e.g., the tree amongst the benches) and object-location (e.g., the tree in the upper left-hand corner of the scene) associations. As participants were not able to predict which type of sample manipulation would be used in any given trial, both of these types of relational associations needed to be retained during the maintenance period in order to detect the non-matching sample *-for a review of relational memory types see* (Konkel et al., 2008). Additionally, during the probe phase, participants could also utilize changes to the configural-relational scene-layout caused by either type of manipulation to detect the non-matching sample. In this type of paradigm, Ryan and Cohen (2004) observed intact preserved memory performance (using eye movements as critical measure) over very short delays, but impaired memory over longer delays. Also, please note, that the term 'configural' processing has been used previously in face-perception literature to denote holistic relational processing of visual information. Here, the term configural-relational refers to the relational (either the spatial, object, or both) aspects of a visual scene in an associative manner that may, though not necessarily, include holistic representation of these relations.

In the test phase of the control conditions, two scene images, both of which were completely different from the sample, were presented side-by-side and subjects were instructed to indicate if the two pictures were the same or different by button press. In half of the trials the pictures were identical and the other half they differed

to the same degree as the probes in the configural-relational DMS condition. The difficulty of discriminating between stimuli was designed to match the configural-relational DMS condition so as to account for any anticipatory activity of difficult choices during the delay. Subjects were instructed that they should not maintain the sample stimulus in memory as this would not help them to make the difficult same/different discrimination during the test phase.

The three conditions were blocked with 20 trials per block. Participants were instructed prior to each block as to which conditions would be tested. It is important to note, that participants were fully aware of the working memory demands prior to the image maintenance necessary to answer successfully at probe. There were 3 blocks per condition, resulting in 60 trials per condition. Presentation of indoor/outdoor stimuli were counterbalanced across each block and were kept constant across trials.
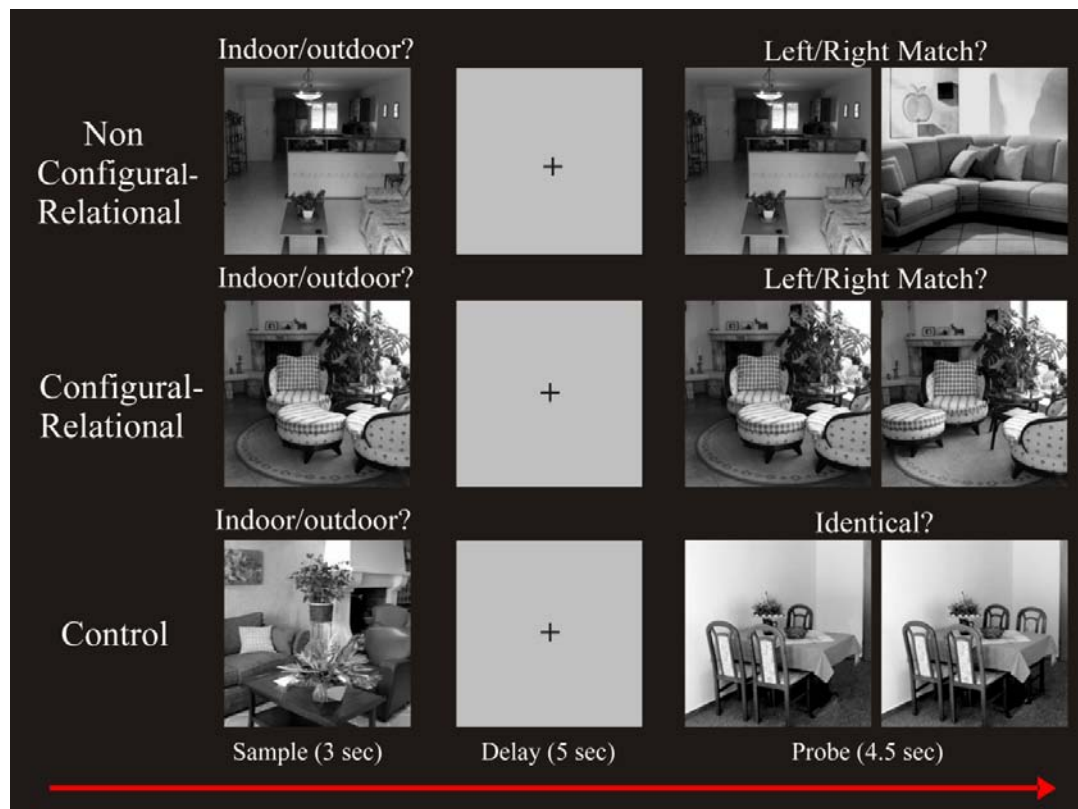
Figure 2.1. Experimental design. An example of a single non-configural-relational delayed-match-to-sample (DMS) trial where participants are instructed to make a deep encoding "indoor/outdoor" judgment at sample and maintain this information over the delay period in order to make a "left/right" match decision at test (top). A single configural-relational DMS trial where the

configuration of items within a scene must be maintained over the delay in order to make a correct decision at test (middle). An example of a single control trial where participants are not required to maintain any stimulus information in order to make a discrimination judgment at test (bottom).

2.4. Behavioural Results 1

2.4.1. DMS task performance.

The three conditions differed in participants' response accuracy during the probe phase (repeated-measures ANOVA; (F (2, 16) = 39.7; p< 0.001). Post-hoc paired t-tests (two-tailed, mean, s.d. - *Bonferroni multiple comparison corrections*) showed that accuracy was better in the non-configural-relational condition (99.3 ± 1.21%) than the configural-relational (69.6 ± 8.15 %, $t(8)$=10.689, p<0.001) and control condition (59.3±13.72%, t(8)=8.265, p<0.001). We were successful in our attempt to match performance in the configural-relational and control conditions as there were no differences in accuracy between these conditions (59.3 ± 4.6% and 69.6 ± 2.7% respectively, $t(8)$ = 1.729, p=0.122). This was important to ensure that any delay activity effects attributed to the configural-relational DMS condition were not due to the anticipation of a difficult judgment/discrimination in the upcoming probe phase. **(Figure 2.2)**

Experiment 1: Accuracy
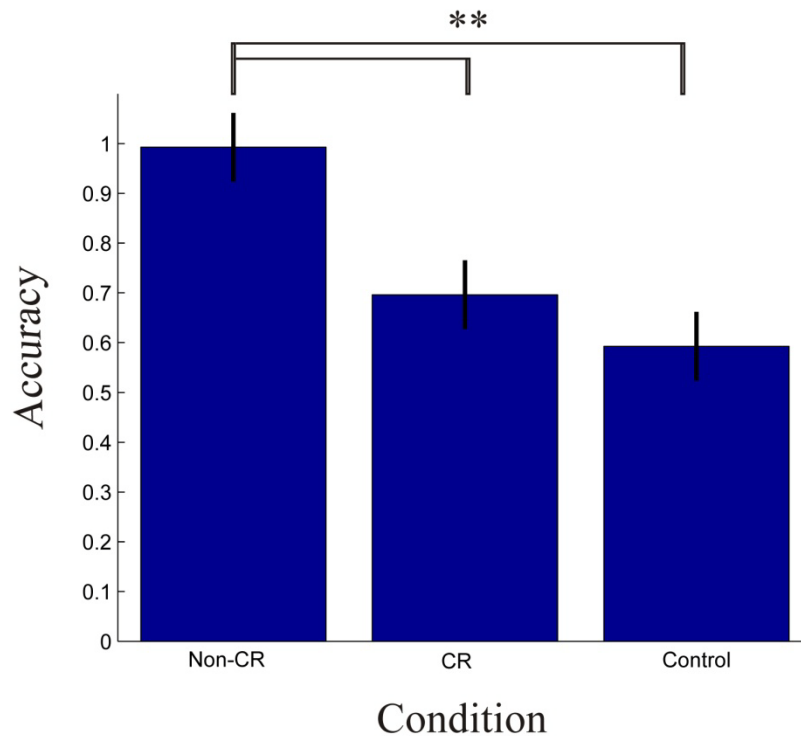
Figure 2.2. Behavioural accuracy results of the delayed-match-to-sample paradigm tested on eight healthy controls in experiment 1. Significant differences were found (**denoting significant differences at the level of p<0.001) for the configural-relational (CR) and Control conditions when compared to the non-configural-relational (non-CR) condition. The CR and control conditions were well matched for accuracy.

A repeated-measures ANOVA also revealed a significant difference between testing conditions for reaction times (RT's) ($F(2, 16) = 49.93$; $p<0.001$). Post-hoc paired t-tests (two-tailed, mean, s.d. - *Bonferroni multiple comparison corrections*) showed significant increases in RTs for configural-relational (2780.77 ± 737.8 ms) when compared to non-configural-relational DMS tasks (913.48 ± 288.2 ms, $t(8) = -8.379$; $p< 0.001$). A similar increase in RTs was found in the control tasks (2055.90 ± 596.1 ms) when compared to non-configural-relational DMS tasks (913.48 ± 288.2 ms, $t(8) = -6.135$; $p< 0.001$). Additionally, participants displayed slower RTs for control tasks compared to configural-relational DMS ($t(8) = 4.870$; $p < 0.01$). **(Fig 2.3)**

Experiment 1:Reaction Time
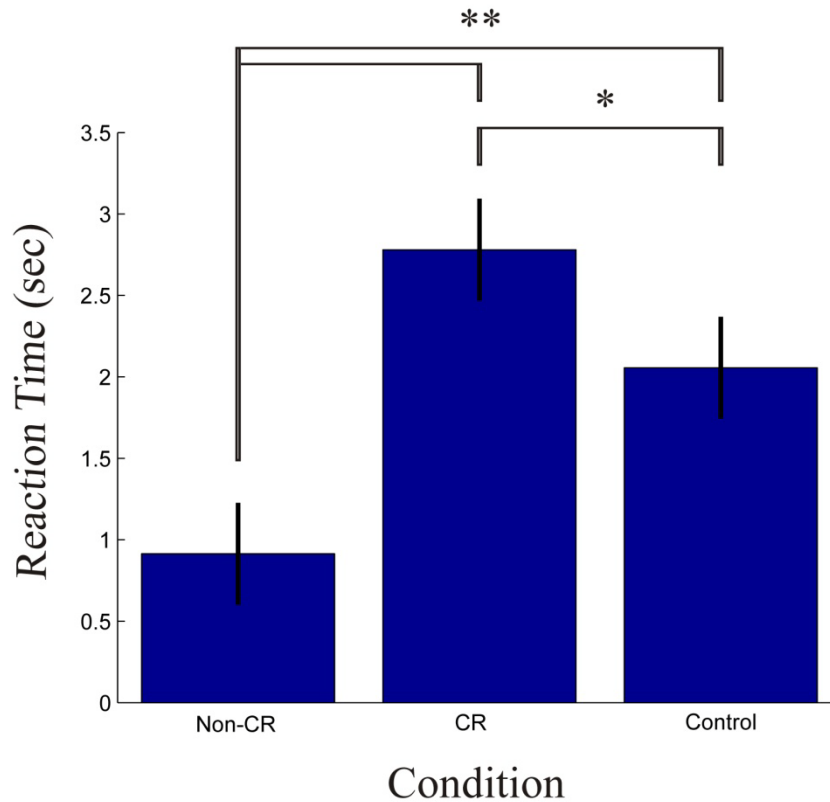
Figure 2.3. Behavioural reaction time results of the DMS paradigm tested on eight healthy controls in experiment 1. Significant differences were found (** denoting $p<0.001$) for the configural-relational (CR) and Control conditions when compared to the non-configural-relational (non-CR) condition. In addition, slower reaction times were found for the control conditions when compared to the CR condition (* denoting significant differences at the level of $p<0.01$).

2.4.2. Behavioural Discussion.

The ability of participants to actively maintain non-configural-relational forms of visual information over delay periods was shown to be easier than the maintenance requirements of retaining the configural relationship between individual elements within the scene (as reflected in accuracy **Fig. 2.2** and speed of response at probe **Fig. 2.3**). Similarly, the perceptual discrimination task performed in the absence of any memory maintenance requirements was shown to be significantly more difficult than the non-configural-relational working memory. It can be argued,

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that there may be a ceiling effect in our current results for the non-configural-relational DMS condition (an issue that will be systematically investigated in Chapter 2), however, the particular design of the current paradigm was to created in order to make direct comparisons of MEG recordings with the control and configural-relational conditions where stimulus content and timing must be identical.

Furthermore, it is important to note that the speed of response (RT) for the perceptual discrimination between similar scenes at probe in the absence of any memory maintenance requirements (control condition) was shown to be significantly faster than the configural-relational condition (**Fig. 2.3**), however, the opposite trend is shown for accuracy (**Fig. 2.2**). This disparity could reflect prior exposure to the image during encoding (and subsequent maintenance) of the configural-relational DMS condition and thereby slightly enhancing accuracy. While the time necessary to visually discriminate between two similar stimuli (control condition) will be shorter than when participants then have to additionally compare this information with the image previously maintained within working memory (configural-relational condition). This issue of perceptual processing and configural-relational maintenance requirements (Lee et al., 2005a; Graham et al., 2006; Shrager et al., 2006) will be discussed in more detail in subsequent chapters (Chapters 4, 5, & 6).

2.5. Magnetoencephalography Methods

2.5.1. MEG Recordings and set-up.

MEG data for all experiments were recorded using a 275-channel CTF Omega whole head gradiometer system (VSM MedTech, Coquitlam, BC, Canada). The parameters in which MEG data are collected is contingent upon the particular frequency bands that are intended to be analyzed. Signals can be properly sampled only if it does not contain frequencies above ½ sampling rate frequency - *see Nyquist sampling theorem* (Nyquist, 2002). If the signal contains frequencies above this critical threshold then, not only is there a loss of phase information, but the sampling of proportionally higher frequencies waves can falsely mimic slower frequency oscillations (i.e. signal aliasing – see **Figure 2.4**). Since our primary aim was to investigate induced oscillatory activity in a relatively low frequency band (Theta: 4-

12 Hz cycles), MEG recordings were collected at 480 Hz sampling rate and with 120 Hz low pass filtering.
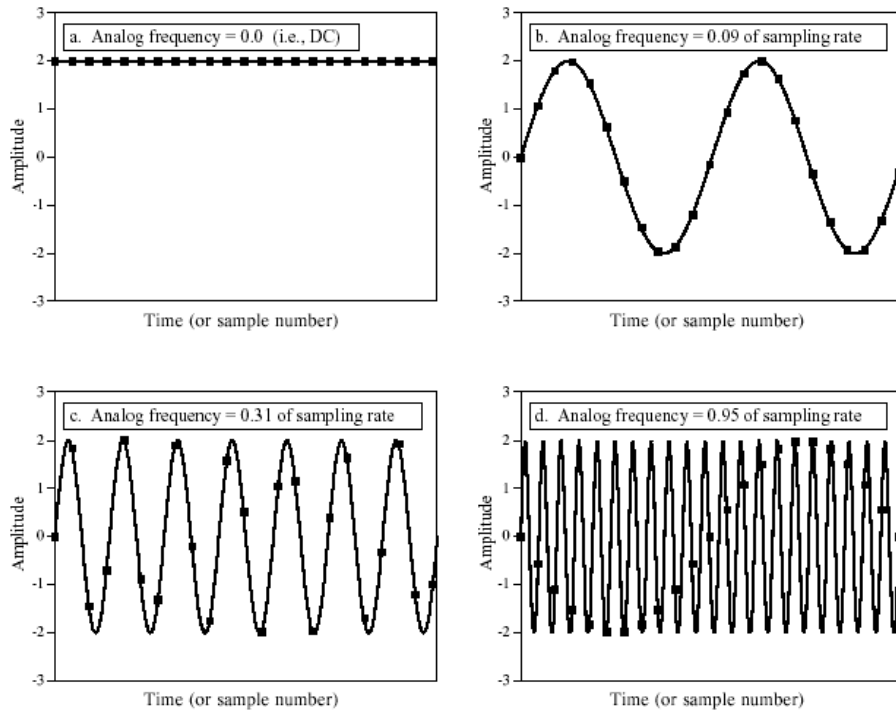
Figure 2.4. Examples of signal aliasing where violations of Nyquist sampling theorem in the selection of the sampling rate at higher frequencies can falsely mimic slower wave frequency oscillations (*Image courtesy of Oxford functional imaging lab, http://users.fmrib.ox.ac.uk*).

After participants were comfortably seated in the MEG, head localizer coils were attached to the nasion and preauricularly 1 cm anterior to the left and right tragus in order to monitor head movement during the recording sessions (**Figure. 2.5B**). The paradigm was projected on to a white screen positioned just in front of the participants and adjusted so as all images were in focus before the start of the experiment.
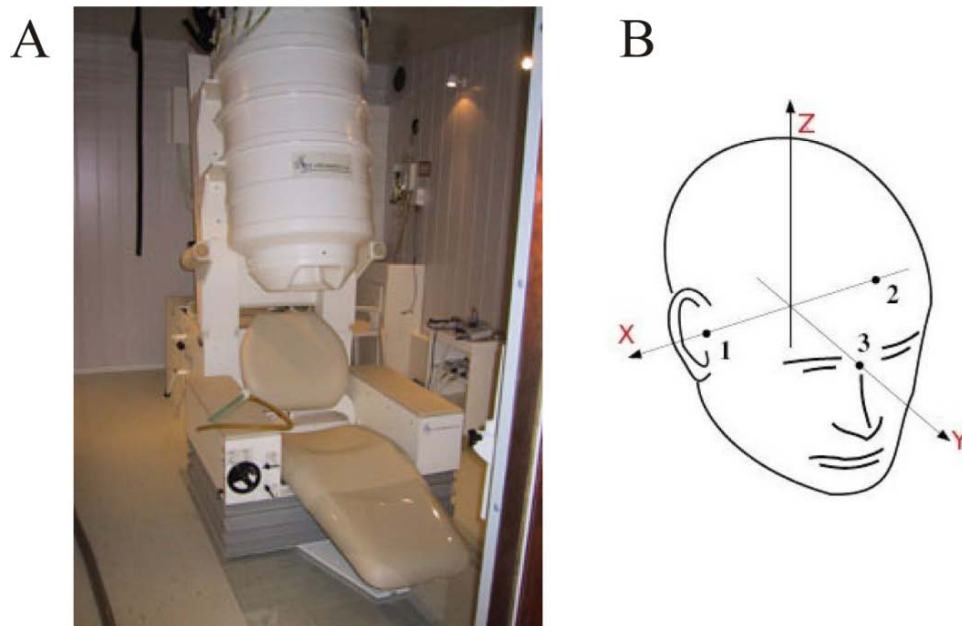
Figure 2.5. (A) The 275-channel CTF Omega whole head gradiometer system located at the Institute of Neurology's Functional Imaging Laboratory of University College of London (*image courtesy of FIL website, www.fil.ion.ucl.ac.uk*). (B) Placement of head-localization coils in order to triangulate head movement during scanning (points 1 & 2 indicate the right and left Preauricular placement and 3 is the *Nasion – image courtesy of INSERM-CEA Cognitive Neuroimaging uni, www.unicog.org*)

2.5.2. Wavelet transformations.

All MEG data were pre-processed with Statistical Parametric Mapping software implemented in Matlab (SPM5; Wellcome Trust Centre for Neuroimaging, Institute of Neurology, London, UK). Butterworth band pass filtering was applied (0.5 – 100 Hz) and reduced to a 140 sampling rate. Data were epoched and then analyzed using continuous single-trial wavelet transformations within the theta band frequency (15 cycle Morlet wavelet transformations with logarithmic scaling between 3-8 Hz) using Matlab based in-house software (Guderian and Duzel, 2005). Single-trial transformations were analyzed separately for amplitude and phase-coupling for each subject in the experiment.

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2.5.3. Phase Coupling Analysis.

To detect functional coupling between sensor groups, a specific subset of wavelets were selected within the theta band (5, 6, 7 Hz) for analysis. Then using continuous single-trial wavelet transformations on unaveraged data (band pass filtered between 3 – 9 Hz; sampling of every 4th time point), phase differences were calculated prior to averaging for each time point of each trial, between all possible sensor combinations of unique sensor pairs and then averaged across trials. Phase alignment for each time point and sensor-pair was measured as the length of the unit phase vector across trials divided by the number of trials. This computation yielded a complex value of phase synchronization ranging from 0 to 1 (Phase locking value (PLV) – *see* (Lachaux et al., 1999). A value of 1 would correspond to perfect phase alignment across trials and a value of 0 to random phase variation across trials (**Figure 2.6**)

Phase-coupling between sensors
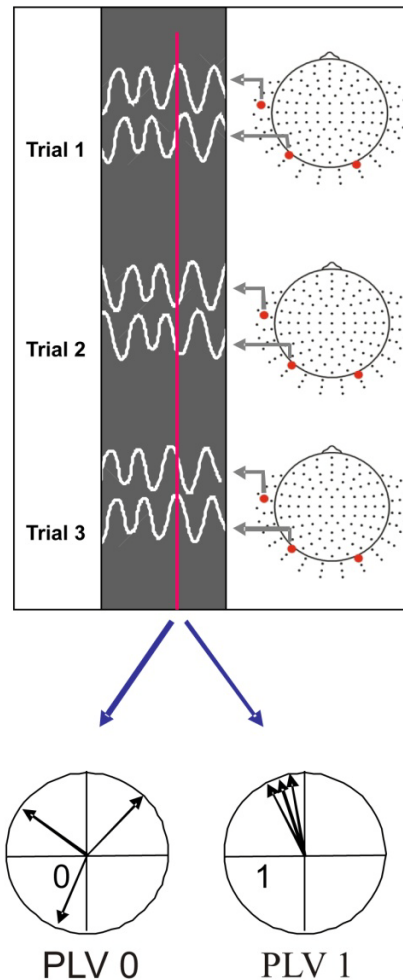
Figure 2.6. An example of phase-coupling measurements between two selected MEG sensors across subsequent recording trials (1-3) within a specified time window. At a given time, a phase-locking value (PLV) is generated ranging from 0 to 1 in order to measure the degree in which two ongoing frequency oscillations are synchronized. Where a PLV = 0 denotes no phase-coupling and a PLV = 1 is perfect phase-coupling between sensors.

The precise timing of patterned neural activity from large-scale cortical assemblies is thought to be captured by MEG recordings in the form of frequency oscillations (Fries, 2005). When the rise and fall of these oscillations from disparate cortical areas are synchronized in time (and within a particular frequency) they are considered to be 'coupled' to the same phase. Theoretically, phase-coupling between different MEG sensor groups reflects the synchronous coordination of these assemblies into a functional cortical network (Fries, 2005).

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Synchrony plots were generated on these transformations contrasting differences in sensor coupling between testing conditions during the delay after correcting for a 500ms pre-stimulus baseline (threshold of $p<0.05$). Sensor groups displaying significant theta synchrony and clustered with at least three other neighbouring significant sensors were chosen for further region of interest analysis using for serial related measures t-tests (threshold of $p<0.05$) to see spatial-temporal changes reveal the magnitude of theta coupling as a function of the experimental manipulation during both sample and delay periods. Phase coupling was not analyzed during the probe phase.

2.6. Magnetoencephalography Results 1

2.6.1. Theta-Phase coupling results.

We performed an unbiased search for theta coupling (6 Hz wavelet) between sensors that were analyzed for all possible combinations of MEG sensors, without an a priori bias. Coupling between two sensors was considered to be significant at a threshold $p<0.05$ per time point if present continuously over three successive theta cycles. Using this approach we found that theta-coupling was stronger in the configural-relational DMS than control condition over left occipital and temporal sensors. Participants' ability to maintain non-configural-relational stimuli in working memory was associated with enhanced phase-coupling over right frontal and parietal sensor groups during delay maintenance compared with the control condition.
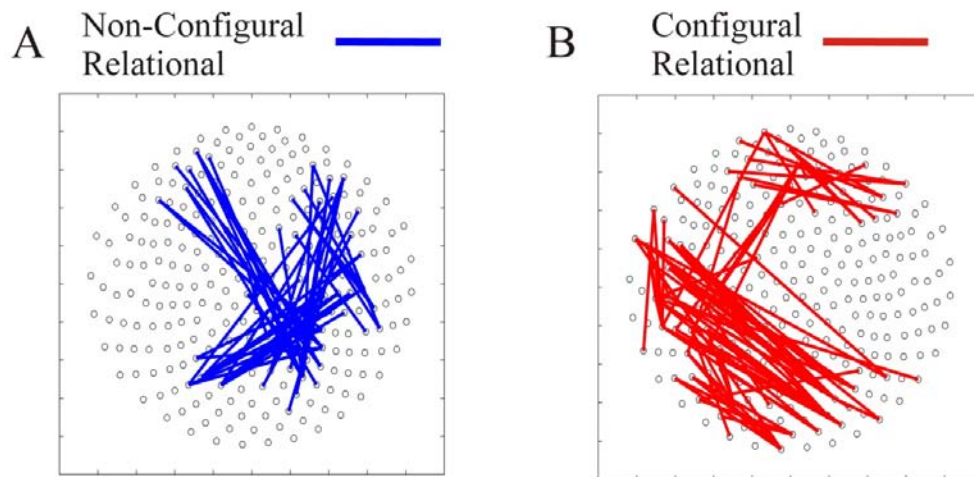
Figure 2.7. Phase coupling analysis using a 6 Hz wavelet (threshold of p<0.05 per time point if present continuously over three successive theta cycles) contrasting experimental conditions displayed in sensor space for experiment 1 comparing configural-relational and non-configural-relational working memory delay periods. In experiment 1, synchrony plots of non-configural-relational delay maintenance (A) display increased right frontal and parietal theta-band sensor coupling (blue) compared to configural-relational delay maintenance (B) which increased left occipito-temporal theta-coupling (red).

This pattern of left occipito-temporal theta synchrony for configural-relational DMS and fronto-parietal theta synchrony for the non-configural-relational DMS also held when directly contrasting the two DMS conditions (**Figure 2.7A** and **2.7B**). To visualize the time course of these characteristic synchrony patterns we plotted the amount of theta synchronization across time (**Figure 2.8**). It can be seen that synchrony between right fronto-parietal sensors is significantly increased for the non-configural-relational condition approximately 1500ms after sample offset and continuing for the rest of the delay period, but remained constant relative to baseline throughout the delay in the configural-relational DMS condition (**Figure 2.8A**). On the other hand, the occipito-temporal sensors showed theta-synchrony elevations throughout much of the sample and delay period for the configural-relational DMS condition while non-configural-relational levels remained at baseline or below (**Figure 2.8B**). Additionally, there was a similar pattern of augmented theta phase-coupling for mid-frontal and left temporal sensors groups for the configural-relational DMS condition (**Figure 2.8C**). However, the fronto-temporal enhancement peaked soon after stimulus off-set while occipito-temporal connectivity

increased during the later portion of the delay. The relative time-courses of augmented theta activity between fronto-temporal and occipito-temporal sensor groups (**Figure 2.8B** and **2.8C**) seem to suggest an interplay of network connectivity that support differential maintenance processes during stimulus presentation and subsequent maintenance of configural-relational stimuli.
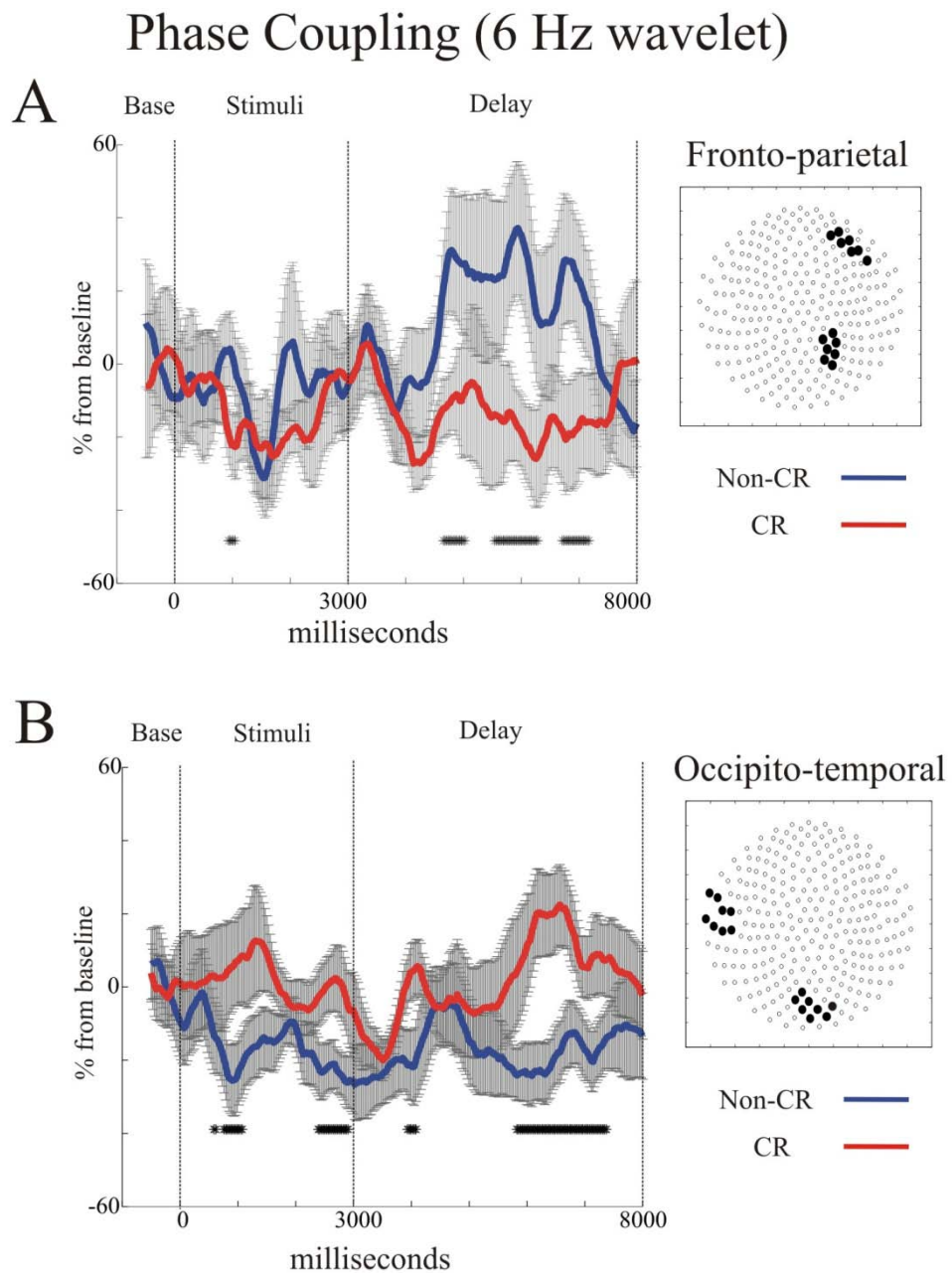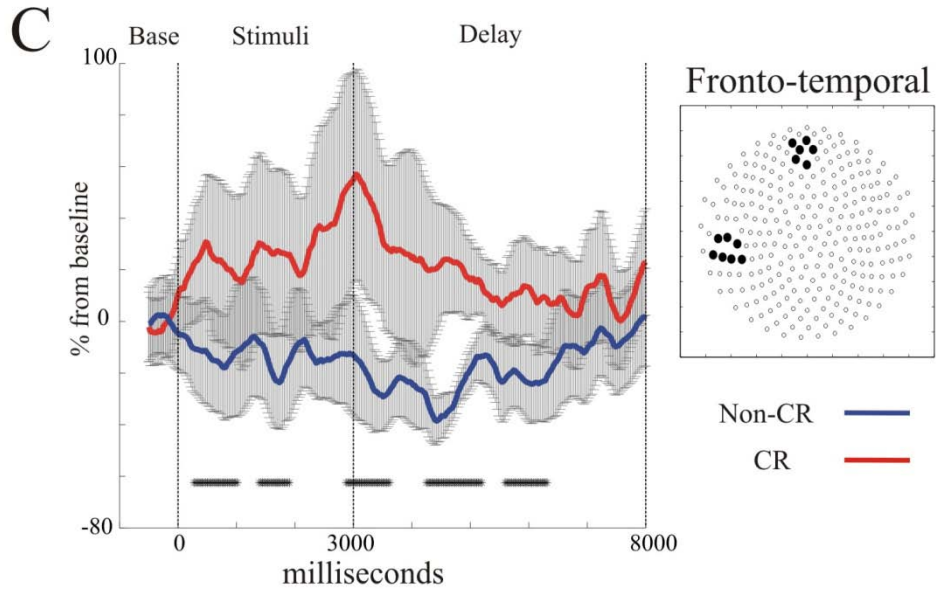
Figure 2.8. Serial measures t-test comparisons of 6 Hz phase-coupling on selected sensor groups (shown on right-side insets) for non-configural-relational ('Non-CR' in blue) vs. configural-relational ('CR' in red) delayed-match-to-sample (DMS) conditions in Experiment 1 (threshold of p<0.05 per time point if present continuously over three successive theta cycles indicated by markings on *x*-axis). Non-configural-relational DMS significantly increased theta synchrony of right fronto-parietal sensor groups during delay periods (A). Alternatively, the configural-relational DMS condition engaged a network of left occipito-temporal (B) and fronto-temporal theta synchrony (C) during stimulus encoding and delay periods.

2.6.2. Theta Amplitude Analysis.

To exclude the possibility that condition differences found in the phase-coupling analysis might be due to parallel differences in theta amplitudes, single trial wavelet transformations were further analyzed using serial related measures t-tests (threshold of p<0.05) on identical sensor groups indicated in the phase-coupling results as having significant differences between conditions. Where as if a specific pattern of wavelet frequencies distinguish between conditions in sensor space for the amplitude analysis in the same direction as the phase-coupling results of the same frequency band then amplitude differences may have biased the phase-coupling signal. Only effects that were significant across at least one entire cycle of the corresponding theta frequency were considered to be reliable; e.g. 200ms for a 5.9 Hz theta oscillation (Guderian and Duzel, 2005).

2.6.3. Theta Amplitude Results.

Importantly, these synchrony patterns were not artefacts due to corresponding theta amplitude differences between DMS conditions. In fact, plots of theta-amplitudes over identical sensor groups either showed no theta amplitude differences (**Figure 2.9A** and **Figure 2.9C**), or showed larger theta amplitudes in the non-configural-relational compared to the configural-relational DMS condition (**Figure 2.9B**). These results are in accord with working memory studies in animals showing that theta-synchrony changes are independent of amplitude differences (Siapas et al., 2005). Thus confirming our findings from Experiment 1 displaying characteristic theta synchrony patterns associated with the differential working memory demands necessary for configural-relational and non-configural-relational maintenance.
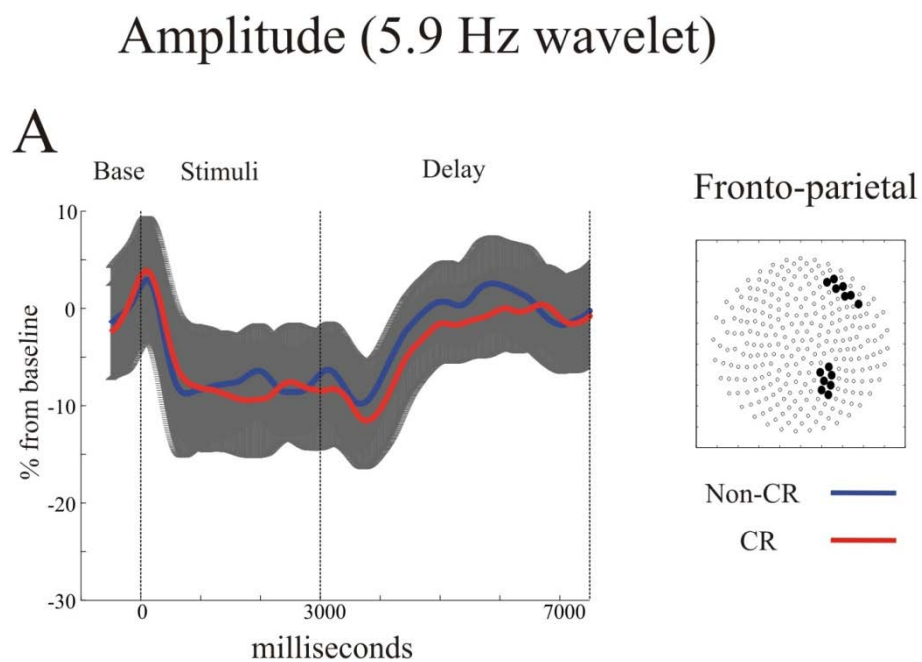
- **Figure 2.9.** *Continued on following page*
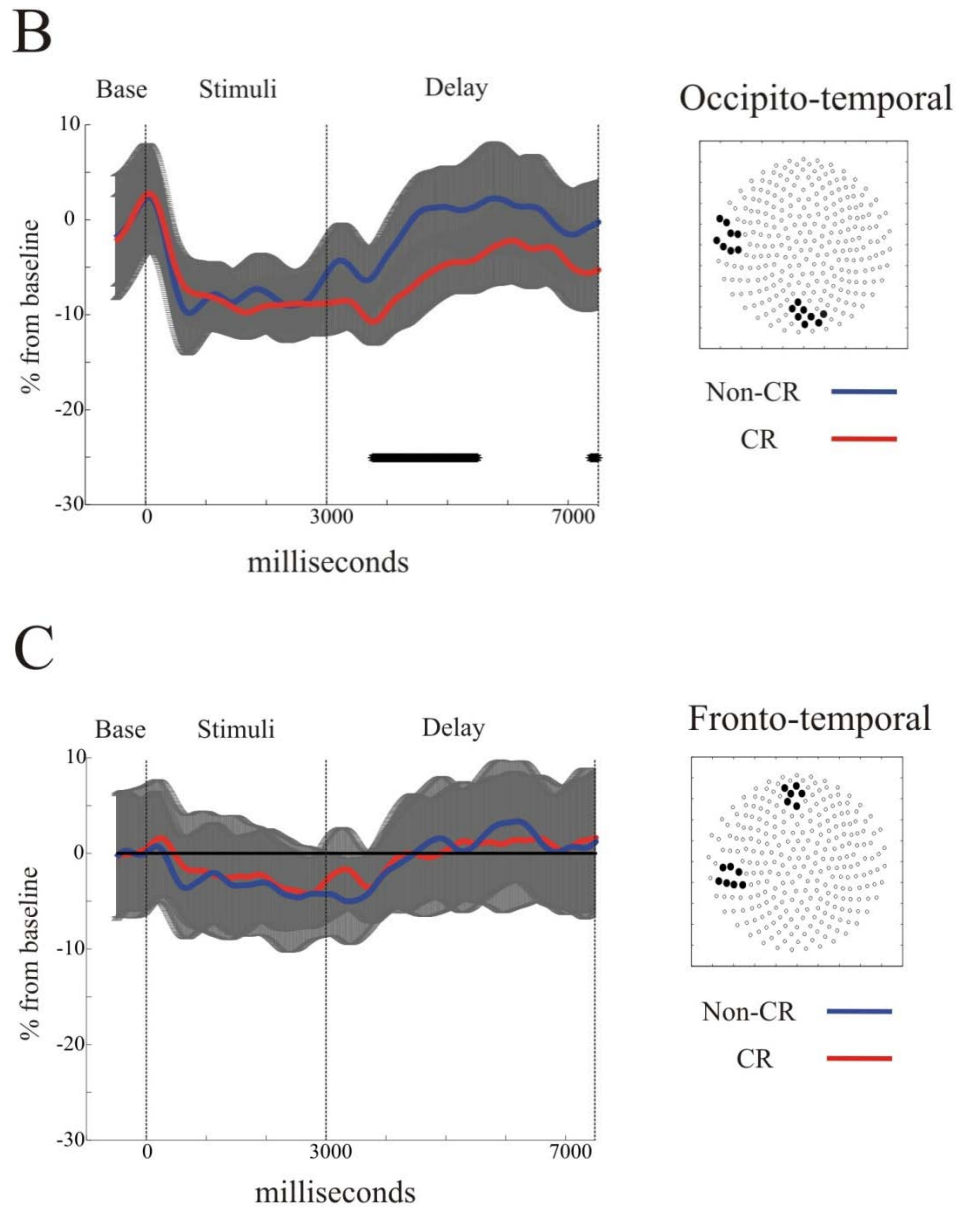
Figure 2.9. Serial measures t-test comparisons plotting the mean theta amplitudes over sensor groups (shown on right-side insets) that were identical to sensor groups that displayed significant theta phase coupling in Fig 2.8 (threshold of $p<0.05$ per time point if present continuously over three successive theta cycles indicated by markings on *x*-axis, error bars indicate s.e.m.). There were either no theta amplitude differences (A and C), or larger theta amplitudes in the non-configural-relational ('Non-CR' in blue) compared to the configural-relational ('CR' in Red) DMS condition (B). This Indicates that theta synchrony cannot be explained by corresponding theta amplitude differences between DMS conditions.

2.7. Discussion 1

Neural synchronization specifically within the theta-band frequency (4-8 Hz) is thought to reflect working memory processes (Jones and Wilson, 2005; Lee et al., 2005b). We investigated the hypothesis that differential theta networks are involved when maintaining the configural relationship of individual elements within a scene when compared to non-configural-relational forms of working memory delay maintenance. Using MEG recordings in healthy participants, we establish that configural-relational and non-configural-relational maintenance can be differentially characterized by induced phase-coupling within the theta band (**Figure 2.7**).

Our results show that the active maintenance of non-configural-relational visual information enhances theta synchrony between right frontal and parietal sensors (**Figure 2.7A**), compatible with earlier studies showing fronto-parietal engagement during working memory delays (Cohen et al., 1997; Courtney et al., 1997; Baddeley, 1998; Sarnthein et al., 1998; D'Esposito et al., 2000; Haxby et al., 2000; Postle et al., 2000; von Stein and Sarnthein, 2000; Deiber et al., 2007). Furthermore, our data suggests that this induced theta activity is functionally (**Figure 2.7A**) and behaviourally (**Figure 2.2**) dissociable from the additional working memory demands of maintaining configural-relational representations. However, if this characteristic shift of theta synchrony patterns (**Figure. 2.7**) are due to a quantitative increase in demands on working memory resources or a qualitative reorganization supporting differential maintenance process, are still yet to be determined (-*see* Chapter 3).

When participants were required to actively maintain the configural relationship of elements with a scene over delay periods, a characteristically different pattern of theta synchronous activity appeared compared to non-configural-relational maintenance (**Figure 2.7**). Enhanced theta coupling of left fronto-temporal sensors emerged during encoding of the stimulus and slowly diminished over the delay period (**Figure 2.8C**). While, increased occipito-temporal theta coupling emerged over the later portion of delay periods (**Figure 2.8B**). Closer inspection of the relative enhancement and decrement of theta coupling between these two sensor combinations over the time course of encoding and maintenance suggest a possible transfer of theta network allocation may occur during working memory retention (*this notion will be explored in Chapters 7 and 8*).

It is important to note that these synchrony patterns did not correspond to theta amplitude changes in the same sensor groups (**Figure 2.9**) complimenting previous work in animals showing that theta-synchrony changes are independent of amplitude differences (Sirota et al., 2008). Furthermore, there is abundant evidence for the possibility that theta oscillations can be generated neocortically in humans (Raghavachari et al., 2001; Caplan et al., 2003). However, a recent study in rodents also suggested that cortically recorded theta oscillations may be volume conducted from the hippocampus (Sirota et al., 2008). Although we cannot exclude this possibility, the fact that the task differences in occipito-temporal theta-synchrony were not accompanied by corresponding changes in theta-amplitudes argues against a volume conduction account.

Recent physiological studies in animals raise the possibility that the coordination of persistent theta activity supporting associative forms of cortical representations during delay maintenance (i.e. configural-relational) are dependent upon hippocampus-dependent slow network oscillations (Buzsaki and Draguhn, 2004; Jones and Wilson, 2005; Sirota et al., 2008). It has be proposed that hippocampus-dependent theta oscillations may coordinate the synchronized activity of different brain regions that represent the multiple scene elements and their locations in space (O'Keefe and Conway, 1978; O'Keefe, 1993). Furthermore, in rodents it has been shown that hippocampally generated theta oscillations (Green and Arduini, 1954; Vanderwolf, 1969) can modify neuronal activity outside limbic areas (Sirota et al., 2008).

During goal-directed behaviour in rodents, medial prefrontal cortical neuronal firing is phase-locked to the hippocampal theta rhythm and this is accompanied by synchronization of the hippocampal and prefrontal theta-rhythms (Jones and Wilson, 2005). This pattern of fronto-temporal theta synchronization is very similar to our current findings during configural-relational stimulus encoding and early maintenance (**Figure 2.8C**). Persist activity in the prefrontal cortex is thought to reflect the tuning of maintenance processes on the current task demands during working memory (Fuster and Alexander, 1971; Goldman-Rakic, 1996; Onton et al., 2005; Deiber et al., 2007), as well as, the resistance to cognitive deviations from those demands (Chao and Knight, 1995; Artchakov et al., 2009). The persistence of fronto-temporal theta synchronization during configural-relational DMS tasks may then reflect similar processes of coordinating attentional working memory resources

to support increases in task demands compared to the non-configural-relational condition (**Figure 2.2**)

Additionally, the occipito-temporal theta synchrony found during configural-relational maintenance may indicate the coordination of cortical representations along the visual ventral stream processing hierarchy. The active maintenance of visual scenes have been shown previously to influence single unit neural firing in visual area V4 of the extrastriate cortex of monkeys that is patterned in time to the particular phase of the ongoing local theta rhythm (Lee et al., 2005b). Although Lee and colleagues did not resolve whether the visual occipital theta rhythm was coupled to medial temporal lobe oscillators, it is very suggestive that the occipito-temporal pattern (**Figure 2.7B**) of theta synchronous activity found here may reflect similar mechanisms. In this way, the hippocampus may contribute to integrating representations of complex conjunctions of scene elements in more rostral portions of the ventral stream, such as the rhinal cortex, with representations of component features in more posterior regions (e.g., visual areas such as V4) (Bussey and Saksida, 2002; Ryan and Cohen, 2004; Aggleton et al., 2007; Hannula and Ranganath, 2008; Harrison and Tong, 2009).

2.8. Summary

Using a delayed-match-to-sample MEG paradigm, we show that configural-relational maintenance engaged stronger theta-coupling between fronto-temporal and occipito-temporal sensor groups during the delay period. While non-configural-relational delay periods were characterized by enhancement of theta-synchrony between right frontal and parietal sensor groups in the absence of configural-relational working memory demands. These results suggest that configural-relational delay maintenance recruits a network of synchronous brain regions driven by theta oscillations that is qualitatively different from non-configural-relational maintenance.

Together, with recent investigations in animals (Jones and Wilson, 2005) and in humans with hippocampal lesions (Olson et al., 2006a; Hannula and Ranganath, 2008; Konkel et al., 2008), these disparate pieces of evidence converge towards the possibility that the hippocampus supports the active maintenance of configural-relational information in working memory by coordinating the synchronization of different cortical regions through theta oscillations. This current study did not allow us to determine the cortical sources of the occipito-temporal synchrony (-*see* Chapter 5) or how this pattern of activity is contingent upon differential increases in working memory demands (-*see* Chapter 3). However, the characteristic topography of this synchrony pattern, its selectivity to configural maintenance demands, as well as previous reports of the dependence of associative forms of working memory on hippocampal integrity (Olson et al., 2006a; Hannula and Ranganath, 2008; Konkel et al., 2008) are very suggestive of such a possibility.

III. Maintenance demands of discrete information

Differential networks of stimulus maintenance can be characterized by theta synchronization of cortical regions during working memory delays. The qualitative demand upon working memory resources to maintain the configural relationship between elements within a scene has been shown to engage a fronto-temporal and occipito-temporal theta network. However, the functional enhancement of this network may reflect the increased number of elements within the scene to be retained and not the qualitative binding of these elements configurally. This chapter will investigate an alternate method of increasing working memory demands quantitatively to determine if occipito-temporal theta synchrony supporting configural-relational maintenance also characterizes generalized increases in working memory demands. By manipulating maintenance requirements by increasing the discrete number of visual information to be held in working memory we can isolate the specificity of theta networks supporting maintenance demands.

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3.1. Introduction

Individuals are rarely required to retain just one single item, such as a picture, in their minds over short delay intervals. The ability of working memory to maintain multiple pieces of transient information, also called 'load', is thought to be a capacity limited process that contributes to a wide variety of cognitive tasks, such as decision making, selective attention, and language (Baddeley, 2003). Furthermore, variations within the population for individual working memory capacity abilities has been thought to be strongly predictive of intelligence and reasoning abilities (Fukuda and Vogel, 2009).

Classically, the storage capacity of working memory has been described as "seven plus or minus two", individual items that can be actively maintained over a short duration (ref). However, later studies have shown this to be an over-estimate, for when participants are not allowed to engage in rehearsal of the items or cannot 'chunk' strings of items into sub-components, then the limited capacity of working memory seems to be approximately four items (Luck and Vogel, 1997; Cowan et al., 2000; Owen, 2004). Furthermore, the complexity (Kane et al., 2006; Xu and Chun, 2006) and/or similarity of the items being stored (Awh et al., 2007), as well as, the allocation of attentional focus on relevant items (Garavan, 1998; McElree, 2001) have been thought to additionally modulate these capacity limits. However, the differential working memory capacity limits of individuals are thought to be regardless if an observer is maintaining a single feature (e.g. colour) or multiple features of the items (e.g. colour and orientation) (Luck and Vogel, 1997).

Recently, two viewpoints have emerged of how working memory capacity limits should be characterized as the amount of cognitive resources: the *discrete resource* or 'slot' model and the *flexible resource* model. The discrete resource model proposes that the storage of individual items are maintained within a discrete number of 'slots' that determine an individual's capacity limit. Therefore, exceeding the resource limits for this fixed number of items will result in subsequent items to not be retained and thus decreasing memory performing above an individual's capacity threshold (Zhang and Luck, 2008). On the other hand, the flexible resource model proposes that working memory resources that determine capacity limits are allocated continuously, where each item shares a relative store of the available

resources and increased item loading thereby decreases the proportion of retentional accuracy for each item (Bays and Husain, 2008).

Both resource models are currently under debate, however, recent EEG recordings have demonstrated possible neurophysiological correlates of these item-limited modulations for average (Vogel and Machizawa, 2004) and individual working memory capacity limits (Fukuda and Vogel, 2009). The rate-limiting factors of working memory storage has been supported by imaging studies observing load- and accuracy- dependant activations in parietal and occipital regions (Vogel and Machizawa, 2004). It has therefore been proposed that these regions of the posterior cortex act as the capacity-limited storage of visual items in working memory (Owen, 2004). As described in Chapter 1, previous evidence showing regions of the pre-frontal cortex specifically tuned to cope with increases in working memory demands (Fuster and Alexander, 1971; Goldman-Rakic, 1996; Jensen and Tesche, 2002; Onton et al., 2005; Deiber et al., 2007; Artchakov et al., 2009) have been proposed to functionally interact with posterior cortical regions to maintain current task demands and goals and resistance to distraction - *in monkeys* (Miller and Cohen, 2001; Artchakov et al., 2009) *and in humans* (Chao and Knight, 1995) – *this notion will be further explored in Chapter 7.*

As demonstrated in Experiment 1, the active maintenance of non-configural-relational visual information enhances theta synchrony between right frontal and parietal sensors (**Figure 2.7A**), which is consistent with earlier studies showing fronto-parietal engagement during working memory delays (Cohen et al., 1997; Courtney et al., 1997; Baddeley, 1998; Sarnthein et al., 1998; D'Esposito et al., 2000; Haxby et al., 2000; Postle et al., 2000; von Stein and Sarnthein, 2000; Deiber et al., 2007). Dynamic adjustments along this network are thought to be modulated in order to compensate for quantitative increases of item retention ('load') during working memory maintenance.

Although the precise nature of working memory's resource limits are still under debate (Bays and Husain, 2008; Fukuda and Vogel, 2009), working memory is by definition a capacity limited process (Baddeley, 2003). Furthermore, it has been proposed that, under certain conditions, long-term memory regions (such as the MTL and specifically the hippocampus) may be engaged to compensate when these capacity limits are exceeded and working memory resources are insufficient for high-load retention -*see* (Shrager et al., 2006) *for a further discussion see Chapters 6*

& 7). Investigations in multi-item working memory load performance in patients with hippocampal lesions have thus far been conflicting, where some report no working memory deficits (Olson et al., 2006a) and others have reported impairments (Aggleton et al., 2007; Axmacher et al., 2007). Additionally, it has remained inconclusive if some reports of hippocampal activation during delay intervals of high working memory load in healthy individuals (Axmacher et al., 2007; Rissman et al., 2008) reflect compensatory short-term maintenance mechanisms (Shrager et al., 2006; Shrager et al., 2008) or are due to the configural-relational nature of the visual stimuli being maintained (Olson et al., 2006a). As demonstrated in Experiment 1, configural-relational maintenance clearly increases demands on working memory resources (**Figure 2.2**) and is contingent upon occipito-temporal theta-coupling (**Figure 2.7**) to support these increases in maintenance demands. However the question still remains, what is the precise nature of these demands on working memory resources?

Experiment 2. Working memory load in normal controls

3.2. Aims 2

The distinct occipital-temporal coupling characterizing configural-relational working memory may reflect the increased demands of quantitatively maintaining a higher number of single elements within a scene (Shrager et al., 2006; Shrager et al., 2008). In accordance with this view, hippocampal engagement (as proposed to be reflected by occipital-temporal theta synchrony) may not be driven by the increased qualitative demands of maintaining the configural relationship between these elements in working memory. Therefore, an alternative method of increasing maintenance demands on working memory is by increasing the number of scenes to be retained over the same delay period in healthy participants. To address this possibility, we investigated the theta-coupling patterns associated with increases in the working memory 'load' from 1 to 3 or 5 scenes to be maintained non-configural-relationally in healthy participants while undergoing MEG recordings. Although, the specific contribution of the medial temporal lobe and the hippocampus to high working memory load cannot be determined in this study (- *this will be further*

investigated in Chapter 7), we can determine if occipital-temporal theta coupling supporting the qualitative demands of configural-relational representations are reflecting the quantitative increases of working memory load.

3.3. Study Design 2

3.3.1. Participants.

Sixteen right-handed healthy subjects (7 male/ mean age 23.2, SD 3.9) participated in the experiment. All participants were recruited from the University College of London's Psychology departmental subject pool and were determined to have no extraneous neurological or psychological disorders that would confound our results. In addition, all eight subjects displayed normal or corrected to normal visual acuity. All participants gave written informed consent to participate and the study was approved by the guidelines of the ethics committee of the University of London Research Ethics Committee for human-based research. All participants were compensated at a rate of £6 per hour for the entirety of the study, which averaged two hours to complete.

3.3.2. Stimuli and Task.

We investigated the theta-coupling patterns associated with increasing the non-configural-relational DMS 'load' from 1 to 3 or 5 scenes to be maintained without the additional demands of configural-relational maintenance (**Figure 3.1**). All MEG recording parameters were identical to those of Experiment 1.

The sample, foil, and probe stimuli consisted of 742 black and white photographs of indoor or outdoor scenes. Scene stimuli were chosen to match the stimuli comparisons with the configural-relational DMS manipulation in Experiment 1. As mentioned previously, a common strategy to enhance working memory retention (i.e. above 3-4 items) is the active verbal rehearsal of the items being retained. In this current study design we are confident that this strategy would not benefit participants performance because of the difficulty of applying verbal "tags" to the stimuli used (**Figure 3.1**). After testing, participants often noted that they attempted verbal rehearsal in the earlier trials of the study then abandoned this

strategy and relied on maintaining the purely visual elements of the scenes. Therefore, the visual working memory loading conditions in this current study were aimed at manipulating just below short-term capacity limits (1, 3 items) and just beyond average capacity thresholds (5 items) (Cowan, 2000; Owen, 2004, Luck and Vogel, 1997).

With this design we also sought to disrupt active maintenance of scenes by task-irrelevant distraction during the delay period. Distracter stimuli consisted of 105 black and white photographs of male and female faces with neutral emotional expression selected from the Karolinska Directed Emotional Faces database (Lundqvist, et al., 1998). In this chapter we will focus primarily on the working memory maintenance without distraction conditions and return to a systematic investigation of task-relevant (Chapter 6) and task-irrelevant (Chapter 7) distraction in later chapters.

Presentation of all indoor/outdoor and male/female stimuli were counterbalanced across each block and were kept constant across individual trials. All pictures were grey scaled and normalized to a mean grey value of 127 and a SD of 75, set at 300x300 pixels, and shown upon a grey background (127 value).
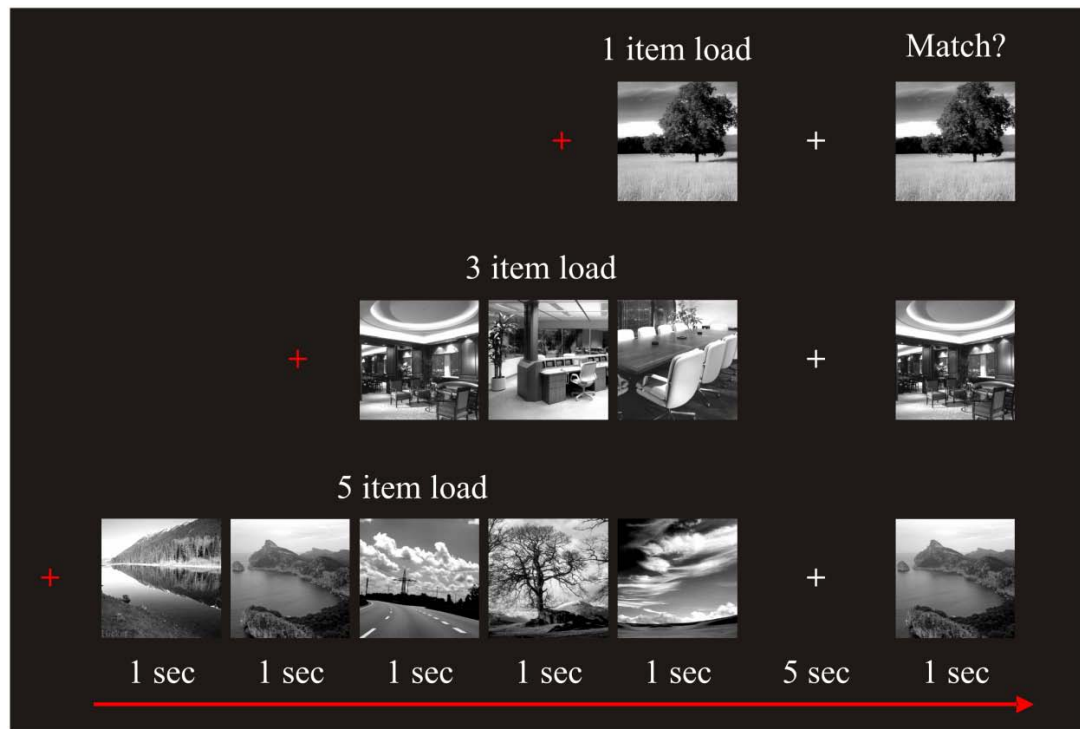
Figure 3.1. Experiment 2 working memory 'load' DMS paradigm. An example of DMS trials where 1 item load (top), 3 item load (middle), or 5 item load (bottom) presented serially must be maintained over a 5 second delay period in order to make a "match" decision at test.

The experiment was a 2x3 factorial design consisting of 7 successive delayed-match-to-sample blocks with 30 trials per block, resulting in 35 trials per condition. The manipulations in this experiment were sample stimulus load of one, three, or five items presented serially for 1 sec duration each. On half of the trials, a face distracter stimuli (1 sec) was presented during the delay period (jittered within a 3 sec window during the middle of the delay). Subjects were instructed to maintain the sample stimuli (1, 3, or 5 items) over a 5 sec delay period whilst fixating on a cross (same retention interval as Experiment 1). At probe subjects were presented with a single picture (1 sec) and asked to indicate by button press using the index or middle finger of the right hand if the picture was a "match" or "non-match" to one of the aforementioned sample stimuli. Targets and foils were randomized and counterbalanced across testing blocks. After which, there was a 3.5 sec inter-trial-interval where subjects were instructed to blink before fixing on the next cue (0.5 sec) (**Figure 3.1**).

3.4. Behavioural Results 2

3.4.1. DMS task performance.

A 2x3 repeated-measures ANOVA (distracter x load) revealed main effects for DMS load on participants' accuracy ($F_{(2,30)} = 26.5$; $p < 0.001$) and their RTs ($F_{(2,30)} = 15.50$; $p < 0.001$), however, there was no effect of distracter stimuli presented during the delay for accuracy ($F_{(1,15)} = 1.49$; $p = 0.24$) or for RTs ($F_{(1,15)} = 0.50$; $p = 0.49$) – *but see Chapter 7*. Pair-wise comparisons of accuracy on load (two-tailed, mean, s.e.m. -*Bonferroni multiple comparison corrections*) displayed differences between 'load 1' vs. 'load 3' ($96.6 \pm 1.1\%$ and $89.1 \pm 2.4\%$, respectively; $t(15) = 3.332$, $p < 0.01$), between 'load 3' vs. 'load 5' ($80.3 \pm 1.9\%$, $t(15) = 3.996$, $p < 0.005$), and between 'load 1' vs 'load 5' items ($t(15) = 9.599$, $p < 0.001$) – **Figure 3.2**.
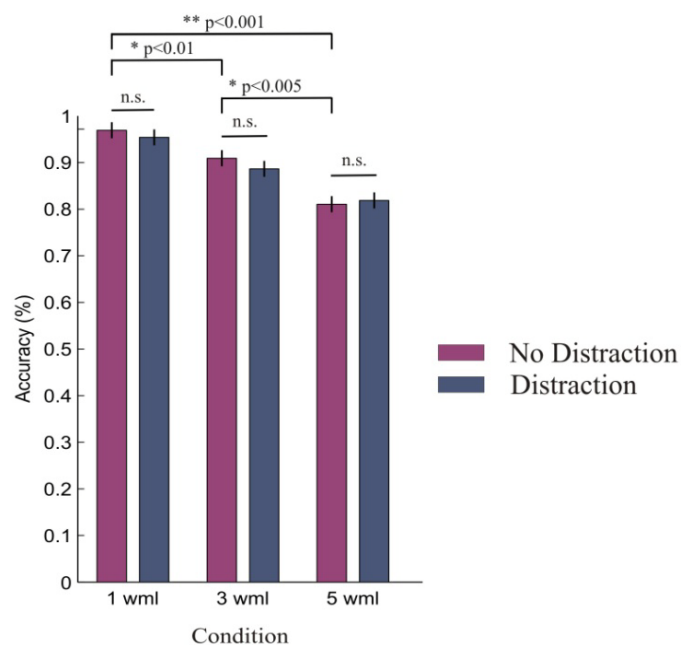
Figure 3.2. Behavioural accuracy results of the working memory 'load' DMS paradigm tested on sixteen healthy controls in experiment 2. We were successful in manipulating working memory 'load' as evident from the accuracy decreases from 1 to 3 items (p<0.01), 3 to 5 items (p<0.005). Working memory performance was seemingly unaffected by task-irrelevant distraction (*see* Chapter 7).

Additional pair-wise comparisons (two-tailed, mean, s.e.m. - *Bonferroni multiple comparison corrections*) showed increased RTs for item load between 'load 1' vs. 'load 3' (924.7 ± 90.1 ms and 1015.3 ± 77.4 ms, respectively; t(15) = -3.772, p<0.005) and 'load 1' vs. 'load 5' (1032.7 ± 78.5 ms, p<0.005) while no RT differences were found between 'load 3' vs. 'load 5' (t(15) = -1.647, p=0.120) **– Figure 3.3**. Post-hoc paired t-test comparisons (two-tailed, mean, s.e.m.) were performed to ensure that no differences for RTs between foils (1034.2 ± 13.8 ms) and targets (1019.7 ± 13.1 ms, *t* (153.4) = 9.39, p=0.35) or between correct (1236.9 ± 28.5 ms) and incorrect responses (1273.4 ± 34.2 ms, *t* (35.9) = -0.82, p=0.41) could inherently bias the effect of DMS load demands on RTs.
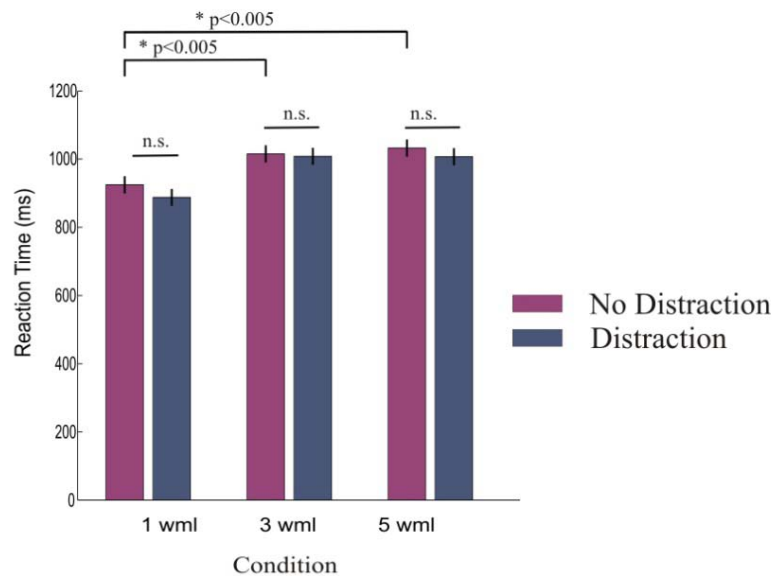
Figure 3.3. Reaction time results of the working memory 'load' DMS paradigm tested on sixteen healthy controls in experiment 2. Significant increases of reaction times were found for 1 to 3 items (p<0.005) and 1 to 5 items (p<0.005). Similar to Figure 2, reaction times were seemingly unaffected by task-irrelevant distraction (*see* Chapter 7).

3.4.2. Behavioural Discussion.

Our attempt to manipulate working memory demands by increasing the number of scenes to remember during delays (load) were successfully reflected in participants' decrease in accuracy as the number of items to remember was increased (**Figure 3.2**). This was further supported by a generalized increase in reactions times (**Figure 3.3**) with increasing load. Consistent with previous reports (Cowan, 2000; Owen, 2004, Luck & Vogel, 1997), when working memory resources are near to the average capacity threshold (i.e. three or five items) the ability to maintain multiple discrete visual elements in working memory steadily decreased when verbal rehearsal was not a beneficial strategy. Furthermore, this significant decrement of performance is a reflection of quantitative increase in working memory demands, which is behaviourally analogous to the qualitative increase in demands of configural-relational scene maintenance found in Experiment 1 (**Figure 2.2**). Consistent with this notion, if the absence of occipito-temporal theta coupling was due to a ceiling effect in the non-configural-relational DMS condition, then high load non-configural-relational maintenance (5 item) where working memory demands are comparatively stressed (yet quantitatively, not qualitatively) should yield similar theta synchrony patterns as configural-relational maintenance.

3.5. Magnetoencephalography Results 2

3.5.1. Theta-Phase coupling results.

Theta phase coupling of increasing memory load demands was investigated using the same methodological procedures as in Experiment 1. Consistent with previous reports (Cohen et al., 1997; Courtney et al., 1997; Baddeley, 1998; Sarnthein et al., 1998; D'Esposito et al., 2000; Haxby et al., 2000; Postle et al., 2000; von Stein and Sarnthein, 2000; Deiber et al., 2007), maintenance of single item working memory load was associated with enhanced theta-synchrony along the fronto-parietal network (**Figure 3.4A**), a synchrony pattern characteristic of the non-configural-relational results in Experiment 1 (**Figure 2.7**) suggesting that results are comparable between these two experiments.

Increasing the number of scene images that had to be retained during the delay from one to five was associated with increased theta coupling of bilateral frontal and temporal sensors (**Figure 3.4B**). This pattern expands on previous EEG studies showing increases in frontal theta-coupling for working memory loading of stimuli such as letter strings (Deiber et al., 2007) and is thought to reflect increasing demands of working memory resources (Fuster and Alexander, 1971; Goldman-Rakic, 1996; Onton et al., 2005; Deiber et al., 2007; Artchakov et al., 2009).   It is important to note, that these results do not claim that fronto-parietal theta engagement is not also occurring during high-load maintenance, but instead that the characteristic synchrony difference compared to low load is significant enhancement of bi-frontal theta coupling.
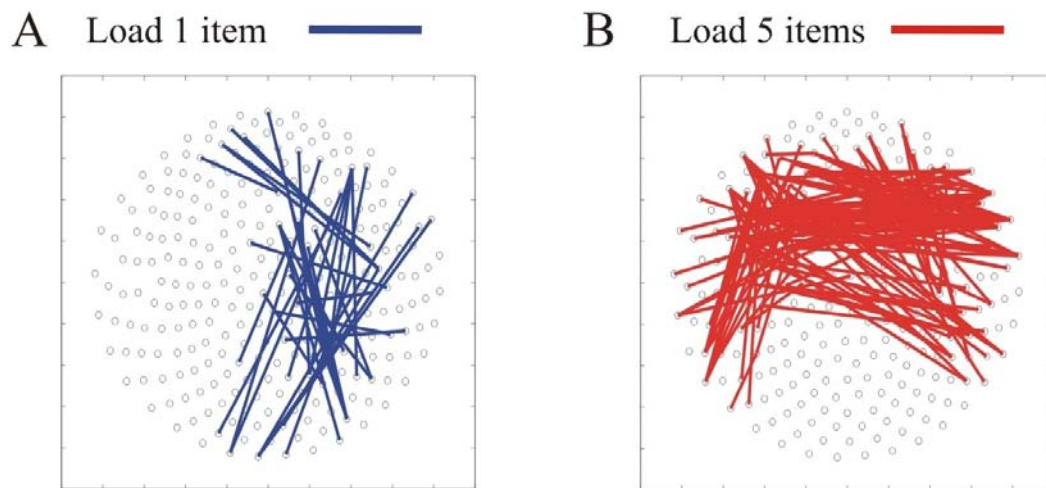
Figure 3.4. Phase coupling analysis using a 6 Hz wavelet (threshold of p<0.05 per time point if present continuously over three successive theta cycles) contrasting experimental conditions displayed in sensor space for Experiment 2 comparing non-configural-relational working memory load. Synchrony plots of 1 item delay maintenance (A) displayed a similar right frontal and parietal theta-phase coupling (blue) as the non-configural task in the previous experiment. While the 5 item delay maintenance (B) increased theta-phase coupling of bi-frontal sensor groups (red), a pattern that is non-overlapping with the configural-relational maintenance sensor coupling.

Most importantly, the bi-frontal theta synchrony due to increased working memory load was completely non-overlapping with the occipito-temporal theta-synchrony of configural-relational maintenance (**Figure 2.7B**), indicating that dissociable networks are responsible for supporting the separate maintenance demands of discrete item loading and configural-relational representations. This effectively rules out the possibility that functional differences between configural-relational and non-configural-relational working memory maintenance are due to quantitative increases in working memory demands, but instead reflect a qualitative alternate mechanism supporting the associative demands of spatial configurations characterized by occipital-temporal theta synchrony.

To visualize the time course of these characteristic synchrony patterns we plotted the amount of theta synchronization across time (**Figure 3.5**). It can been seen that for both low load (**Figure 3.5A**) and high load (**Figure 3.5B**) condition the characteristic theta coupling for these conditions (front-parietal and bi-frontal, respectively) was already engaged during encoding, then this synchrony persisted across the retention period. Consistent with Experiment 1 (**Figure 2.8**), this suggests that delay period theta synchronization is actively replaying the encoded precept during working memory maintenance upon a theta-networks already engaged by stimulus off-set during encoding (for discussion of working memory 'replay' – see Supplementary Discussion, Chapter 5). Furthermore, it is interesting to note that bi-frontal theta-coupling reaches an apex in the early portion of the delay (~1000 ms) then declines to baseline by the later portion of the delay. Although this was not directly investigating this study, these synchrony changes are suggestive of a possible differential switching of theta networks engagement across long retention periods (i.e. 5 seconds) in order to support increasing demands of high working memory load (**Figure 3.5B**) or configural-relational maintenance (**Figure 2.8B & 2.8C**). – *this notion will be discussed further in Chapter 7.*

A   Phase Coupling (6 Hz wavelet)
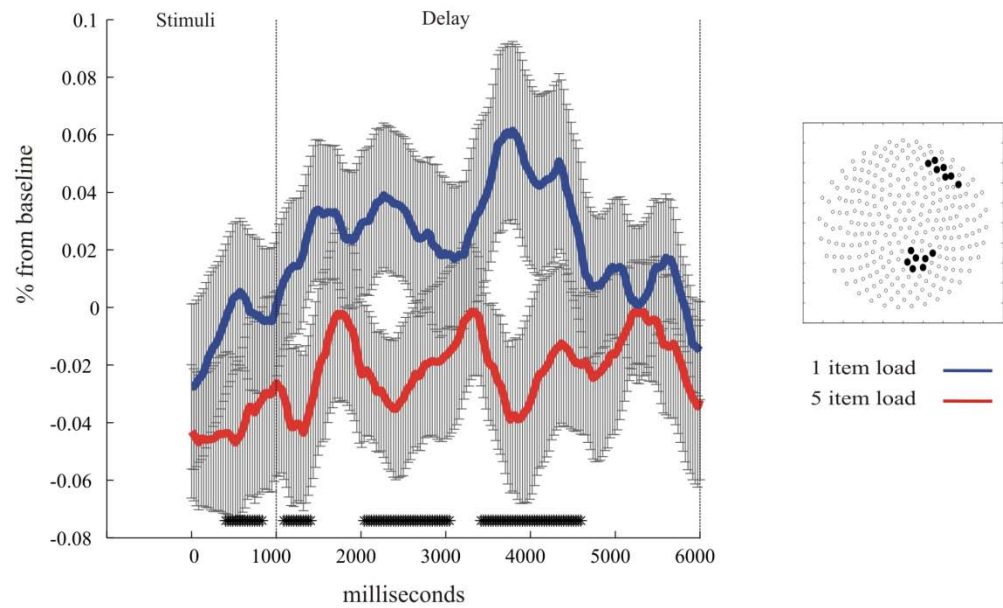
B   Phase Coupling (6 Hz wavelet)
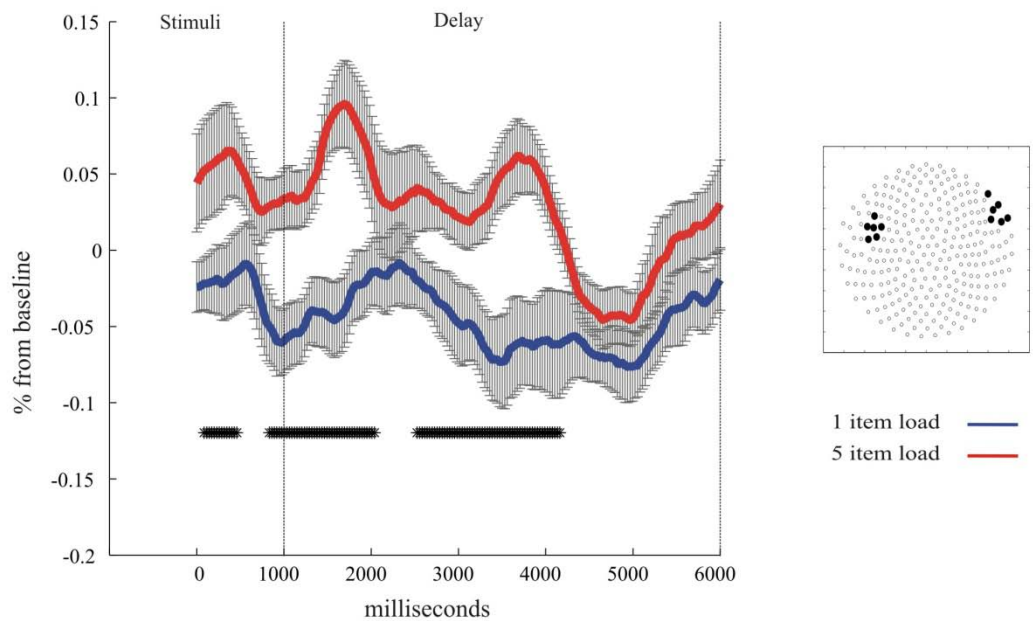
Figure 3.5. Serial measures t-test comparisons of 6 Hz phase-coupling on selected sensor groups (shown on right-side insets) for non-configural-relational low working memory load ('1 item load' in blue) vs. high working memory load ('5 item load' in red) delayed-match-to-sample (DMS) conditions in Experiment 2 (threshold of p<0.05 per time point if present continuously over three successive theta cycles indicated by markings on *x*-axis). Similarly to the non-configural-relational condition of Experiment 1, low working memory load

significantly increased theta synchrony of right fronto-parietal sensor groups during delay periods (A). Alternatively, the high working memory load condition engaged a network of bi-lateral and left temporal theta synchrony (B) during stimulus encoding and delay periods. A pattern that is completely non-overlapping with the configural-relational maintenance theta engagement of Experiment 1.

3.6. Discussion 2

These results shed light on the differential engagement of theta synchronous networks supporting increases of working memory maintenance demands. Quantitative increases in maintaining a high load of discrete visual elements in working memory was characterized by theta-coupling of bi-frontal sensor groups (**Figure 3.4B**). This modulation of increased frontal coupling as function of working memory load is in accordance with the notion that increased engagement of the PFC is thought to reflect increasing demands of working memory resources (Fuster and Alexander, 1971; Goldman-Rakic, 1996; Onton et al., 2005; Deiber et al., 2007; Artchakov et al., 2009). In contrast, the engagement of occipito-temporal theta-coupling is a dissociable network supporting the qualitative demand increases of maintaining the configural relationship of individual scene elements (**Figure 2.7B**). Although both processes tax working memory resource demands as reflected by participants' behavioural performance, the functional networks associated with these two forms of maintenance are topographical dissociable. As well as, display recruitment of alternate theta networks for additional resource allocation compared to the "classic" fronto-parietal network (Cohen et al., 1997; Courtney et al., 1997; Baddeley, 1998; Sarnthein et al., 1998; D'Esposito et al., 2000; Haxby et al., 2000; Postle et al., 2000; von Stein and Sarnthein, 2000; Deiber et al., 2007) supporting low demand working memory (**Figure 3.4A & 2.7A**).

In this current study we did not find modulations along parietal and occipital regions (Cowan et al., 2000; Owen, 2004; Fukuda and Vogel, 2009) of frontal sensors with increasing working memory load. Our current data did not support the notion that frontal regions functionally interact with posterior cortical regions to maintain current task demands and goals (Chao and Knight, 1995). Although, this was not the specific aim of this experimental manipulation, it is curious that functional engagement along the frontal-parietal (and occipital regions) was not

enhanced with systematic increases of load (Cowan et al., 2000; Owen, 2004; Fukuda and Vogel, 2009). However, this was most likely due to the design of theta coupling comparisons between conditions in sensor space, where synchrony pattern differences were contrasts and there-by displaying significant 'differences' in activity. Therefore, it is likely that qualitative increases in stimulus loading strengthened theta-coupling along frontal-parietal (and occipital regions) maintenance network, but this enhancement was below the significance threshold chosen for this comparative analysis. Never the less, the robust bi-frontal engagement was the most significant network distinguishing high-load from low-load maintenance within this experimental design. The nature of this bi-frontal coupling in high-load maintenance and its relationship to delay distraction will be explored further in Chapter 7.

Our findings are in accordance with recent studies of patients with amnesia due to medial temporal lobe (hippocampal) damage displaying selective impairments in the ability to maintain relational conjunctions in working memory but had no memory load related impairment (Olson et al., 2006b; Finke et al., 2008). Although this anatomical distinction and the contribution of the hippocampus to these theta synchrony patterns could not be determined in Experiments 1 or 2 (*but see Chapter 5 and 7*), our current results suggest a possible anatomical dissociation contributing to distinct theta networks supporting increased working memory maintenance demands.

3.7. Summary

In experiment 2, we sought to increase demands on working memory maintenance resources by quantitatively increasing the number of individual scenes to be retained. High load maintenance (compared to low load) was characterized by theta-coupling of bi-frontal sensor groups. This pattern of engagement was functionally dissociable from the occipito-temporal theta-coupling supporting the maintenance demands of configural relationships during working memory delays. Furthermore, both of these maintenance demands topographically differed from the "classic" fronto-parietal working memory network which characterized low load (Experiment 2) and non-configural-relational (Experiment 1) delay maintenance. Although, the specific contribution of the medial temporal lobe and the hippocampus to either of these forms of working memory demands could not be determined in this study, the topographical engagement of theta coupling of these two networks are clearly dissociable. The anatomical relationship (MTL) of these theta synchrony patterns to the differential working memory demands will be investigated in later chapters (Chapters 5 & 7). Specifically, the contribution of hippocampal integrity to configural-relational working memory maintenance and occipito-temporal theta synchrony.

IV. Working memory deficits in patients with epilepsy

The hippocampus and surrounding medial temporal lobe structures have long been held to be critical for long-term declarative memory but not for short-term or working memory. The notion that patients with selective and bilateral medial temporal lobe lesions have intact short-term memory has been a key argument to support the classical distinction between long-term memory and working memory. Recent behavioural and electro-physiological evidence, as well as, the results from Experiments 1 and 2, have begun to challenge this classical distinction. Converging evidence now suggests that the ability to maintain configural-relational information in working memory for periods as short as a few seconds critically depends on the hippocampus. In functional terms, the hippocampus may be necessary for coordinating maintenance when it relies on distributed cortical representations of objects, locations and their conjunctions.

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4.1. Introduction

As discussed in Chapter 1, the ability to retain events over very brief intervals of time (short-term memory) has been thought to be anatomically and functionally distinct from mechanisms necessary for lasting memories (long-term memory). However, ecent reports of patients with selective hippocampal atrophy displaying working memory impairments for the spatial relationship of objects over short delay periods (Hannula et al., 2006; Olson et al., 2006a) suggests that the hippocampus may contribute to the configural-relational DMS task performance in Experiment 1. Furthermore, the characteristic topography of occipito-temporal theta synchronization found during configural-relational delay maintenance suggests that the hippocampus is necessary for the functional coordination of these cortical regions in order to support the maintenance of the configural relationships within a scene. Having established that this theta network is functionally dissociable from quantitative increases in working memory maintenance demands (Experiment 2), we next sought to investigate our hypothesis that configural-relational working memory is behaviorally dependent on hippocampal integrity. To this end, we tested the configural-relational working memory performance of patients with bilateral hippocampal sclerosis (BHS) due to epilepsy. Patients with left temporal lobe epilepsy determined to be 'MRI-negative' for hippocampal reductions (LTN), served as a control group to match the effects of recurrent epileptic seizures and antiepileptic medication in BHS patients, but without hippocampal sclerosis.

Furthermore, we will determine if configural-relational working memory performance is due to any contributing factors of the patients' abilities of perceptual discrimination. These tasks were performed while patients underwent MEG recordings to determine theta synchronization during working memory maintenance periods, however, this chapter will primarily focus on the behavioural and structural characterization between these two cohorts of epilepsy patients (-see Chapter 5 for investigation of delay maintenance theta synchronization of epilepsy cohorts).

Experiment 3A. Configural-relational working memory in bilateral hippocampal sclerosis

4.2. Aims 3A

We will first characterize two epilepsy patient cohorts for subsequent working memory testing. Our 'test' cohort consisted of six patients with bilateral hippocampal sclerosis (BHS) and our 'control' cohort are six patients with left temporal lobe epilepsy determined to be 'MRI-negative' for hippocampal reductions (LTN). We then tested patients on a slightly modified version of the DMS paradigm used in Experiment 1 to determine if BHS patients display selective impairments in configural-relational DMS conditions and if this impairment is due to deficits in perceptual discrimination.

4.3. Study Design 3A

4.3.1. Patient groups.

Bilateral Hippocampal Sclerosis (BHS).

Nine patients with temporal lobe epilepsy and Bilateral Hippocampal Sclerosis (BHS) were recruited for this study. Three BHS patients were excluded from the final analysis: LH004 couldn't perform the DMS task (leading to the paradigm modifications outlined in the *Stimuli and Task* section below), AJ003 was excluded due to indications of diagnosis co-morbidity (possible Asbergers Syndrome), and AB025 was excluded due to left hand dominance, which can obfuscate results of the phase-coupling synchrony analysis (see Chapter 5). Therefore, the final BHS test cohort consisted of 6 right-handed patients (2 female/ mean age 43.2; SD 9.8).

Left Temporal Lobe Epilepsy (LTN).

The control group consisted of 6 right-handed patients with left Temporal Lobe Epilepsy (LTN) (2 female/ 37.2; SD 11.4) with normal structural MRI scans (**Figure 4.2**). This LTN group was chosen in order to match the effects of recurrent epileptic seizures and antiepileptic medication of the BHS cohort, whilst comparing structurally intact hippocampi (LTN) to patients with bilateral hippocampal sclerosis (BHS) (**Table 4.1**).

4.3.2. Characterization of patient groups.

All patients were attending clinics of the Department of Clinical and Experimental Epilepsy of UCL Institute of Neurology and the National Hospital for Neurology and Neurosurgery. Two experienced neurologists reviewed the seizure characteristics and current medications of both epilepsy groups investigated in this study and were determined to be comparable between groups (**Table 4.1**).

In addition, 11 normal controls (NC) participated in a behavioural version of the same experiment (4 male/ mean age 24.7; SD 3.9). All NC participants were recruited from the University College of London's Psychology departmental subject pool and were determined to have no extraneous neurological or psychological disorders that would confound our results. In addition, all subjects displayed normal or corrected to normal visual acuity. All participants gave written informed consent to participate and the study was approved by the guidelines of the ethics committee of the University of London Research Ethics Committee for human-based research. All participants were compensated at a rate of £6 per hour for the entirety of the study, which averaged two hours to complete.

Subjects	Dx	DOB	Seizure Onset	Seizure type	Seizure Freq	Medications
DH006	BHS	15/02/1962	17 yrs	cps	3x week	Lev 1250mg od; Cbz 200mg od
EM011	BHS	26/08/1983	4 yrs	cps	1x month	Pgb 675mg od; Cbz 1200mg od; Ace 500mg od; Flx 20mg od
GP013	BHS	31/08/1957	3 yrs	cps	2x month	NaVPA 1000mg bd; Phy 450mg bd; Lev 2500mg bd; Clob 10mg tds
TC016	BHS	21/12/1965	10 yrs	cps	1x month	Cbz 1800mg od; Tpm 200mg od; Prm 500mg od
TE015	BHS	08/01/1958	9 yrs	cps	1-2x month	Lev 1000mg bd; Cbz 600mg bd; Pgb 250mg bd
M_R	BHS	01/08/1963	37 yrs	cps & sgs	2-3x week	Cbz 700mg bd; Pgb 300mg bd; Lmt 150mg bd
SC005	LTN	22/04/1980	6 yrs	cps	1x month	Cbz 1000mg bd; Lev 1000mg bd; Lmt 150mg bd
RG014	LTN	24/12/1954	21 yrs	cps	0-6 x month	Cbz 400mg tds; Prm 250mg tds; Clon 0.5mg od
FT026	LTN	15/09/1980	5.5 yrs	cps	2-4x month	Lev 1 g bd; Lmt 300 mg bd
H_P	LTN	06/09/1959	11 yrs	cps	2-3x day	Lev 1300mg bd; Phy 150mg bd; Prop 40mg od; Lof 70mg bd
NM021	LTN	12/02/1974	18 yrs	cps	1x hour	Lev 1500mg bd; Clob 20mg od
SN010	LTN	20/01/1975	23 yrs	cps & sgs	1x month	Lmt 200 mg bd; Pgb 50 mg bd

Table 4.1. Demographic information for bilateral hippocampal sclerosis patients (BHS) and left temporal lobe epilepsy patients with normal MRI (LTN). Seizure type: complex partial seizures (cps), generalized seizures (sgs).

Medication: Acetazolamide (Ace), Carbamazepine (CBZ), Clobazam (CLB), Clonazepam (CLN), Lamotrigine (LTG), Levetiracetam (LVT), Lofepramine (Lof), Phenytoin (PHT), Pregabalin (PGB), Primidone (PMD), Propranolol (Prop), Sodium Valproate (VPA), Topiramate (TPM).

All patients underwent comprehensive clinical whole brain MRI scans including: T1-weighted, proton density, T2-weighted and FLAIR acquisition protocols. These images were reviewed by two experienced consultant neuroradiologists who found no structural abnormalities other than bilateral hippocampal sclerosis in the BHS group (see **Figure 4.1** for T1-weighted images showing isolated bilateral hippocampal atrophy in BHS patients M_R, DH006, and EM011. See **Figure 4.2** for BHS patients TE015 and visual comparison of LTN patient FT026 with normal appearing hippocampi). Unfortunately, T1-weighted images could not be obtained for visual demonstration purposes for BHS patients GP013 and TE015 because they were scanned at an alternative site. We are confident that the comprehensive review of structural MR imaging by consultant neuroradiologists confirms that these patients (BHS) have isolated hippocampal injury and there is no structurally visible damage to extra-hippocampal medial temporal lobe structures.
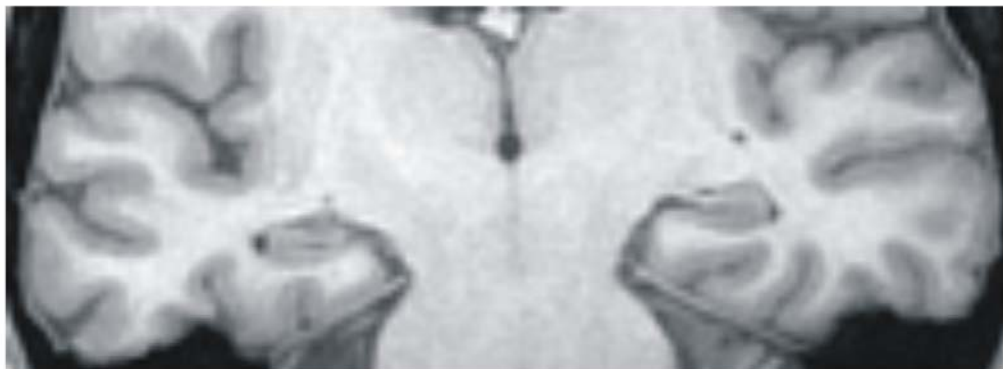
Patient (BHS): M_R

- **Figure 4.1.** *Continued on following page.*
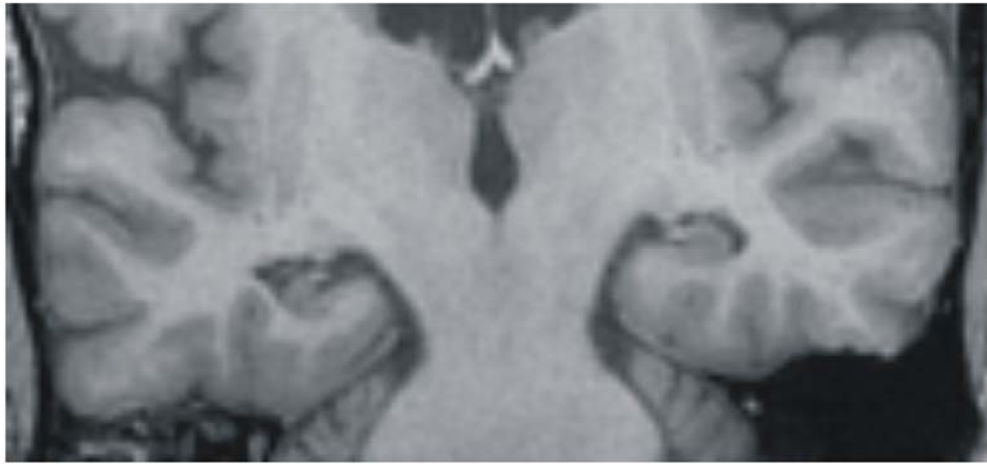
Patient (BHS): DH 006
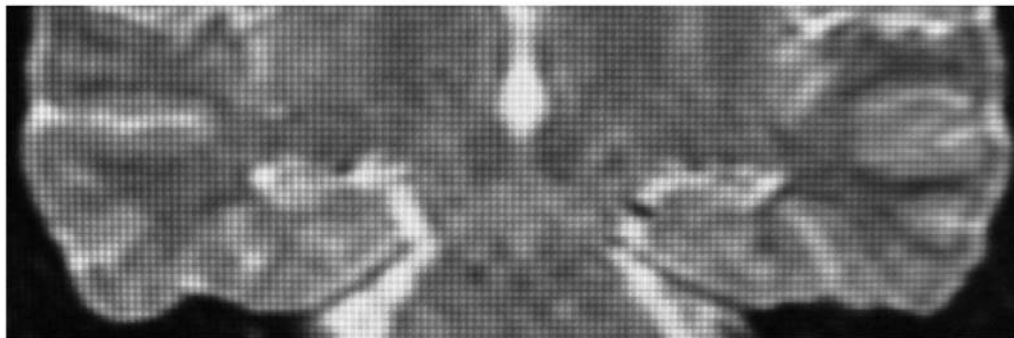
Patient (BHS): EM 011

Please note- digital image taken from hard copy film

Figure 4.1. T1-weighted images showing isolated bilateral hippocampal atrophy in BHS patients M_R, DH006, and EM011 (See Figure 3.2 for BHS patient TE015). No images were available for BHS patients GP013 and TE015.

Hippocampal volume measurements for all BHS and LTN patients were assessed according to an atlas-based volumetric technique (Woermann et al., 1998) and were conducted as standard diagnostic intake of the Department of Clinical and Experimental Epilepsy of UCL Institute of Neurology and the National Hospital for Neurology and Neurosurgery (*Hippocampal volumes in this study we retrieved via database and were not performed by the candidate*) – see **Table 4.2**.

One-way ANOVAs comparing hippocampal volumes of BHS and LTN patients confirmed bilateral volume differences (Right Hippocampus: ($F_{(1, 9)}$ = 29.64; $p<0.001$) & Left Hippocampus: ($F_{(1, 9)}$ = 31.98; $p<0.001$). Independent t-

tests (two-tailed, mean, s.e.m.) confirmed substantial bilateral hippocampal reductions in the BHS group compared to LTN patients (BHS right hippocampal volume (1.834 ± 0.195 cc) vs. LTN right hippocampal volume (2.933 ± 0.089 cc; $t(9) = -5.444$, p<0.001) & BHS left hippocampal volume (1.502 ± 0.210 cc) vs. LTN left hippocampal volume (2.925 ± 0.150 cc; $t(9) = -5.655$, p<0.001) – *see* **Figure 4.2** *for visual comparison of BHS patient TE015 and LTN patient FT026*. Hippocampal volume data were not available for one patient with BHS.

Independent t-tests (two-tailed, mean, s.e.m.) confirmed that there were no group differences between BHS and LTN patients in regards to age (BHS 44.3 ± 3.87yrs, LTN 38.33 ± 4.60 yrs, $t(10) = 0.998$, p=0.342), age of seizure onset (BHS 13.3 ± 5.16 yrs, LTN 14.08 ± 3.17, $t(10) = -0.125$, p=0.903) performance IQ (BHS 92.00 ± 9.77, LTN 102.75 ± 6.34, $t(6) = -0.923$, p=0.392), and working memory digit span (*scaled scores derived from the sum of strings recited forward and backward*, BHS 9.50 ± 1.06, LTN 8.75 ± 2.14, $t(8) = 0.350$, p=0.735) (**Table 4.2**).

Subject	Dx	Volume_R	Volume_L	VIQ	PIQ	Digit span (WM)
DH006	BHS	1.44	0.95	104	87	11
EM011	BHS	2.47	1.8	113	116	12
GP013	BHS	*	*	93	*	11
TC016	BHS	1.83	1.96	84	36	8
TE015	BHS	1.42	1.04	96	*	10
M_R	BHS	2.01	1.76	80	69	5
SC005	LTN	3.04	3.32	97	106	*
RG014	LTN	3.02	2.88	*	*	*
FT026	LTN	2.68	2.8	102	*	8
H_P	LTN	3.27	3.41	107	119	12
NM021	LTN	2.75	2.5	70	90	3
SN010	LTN	2.84	2.64	96	96	12

Table 4.2. Hippocampal volumes and selected neuropsychological testing used for exclusionary criteria for bilateral hippocampal sclerosis patients (BHS) and left temporal lobe epilepsy patients with normal MRI (LTN). Hippocampal volumes are reported in cubic centimetres. Digit span (scaled scores derived from the sum of strings recited forward and backward): < 5=impaired, 9-11 mid average 12-13 high average. * Note some data missing.

A Left Temporal Lobe Epilepsy
'MRI-negative' for hippocampal atrophy
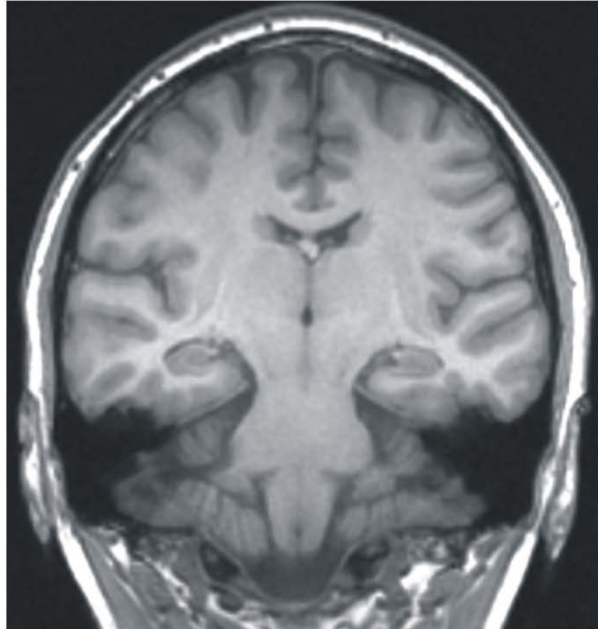
Patient (LTN): FT 026

B Bilateral Hippocampal Sclerosis
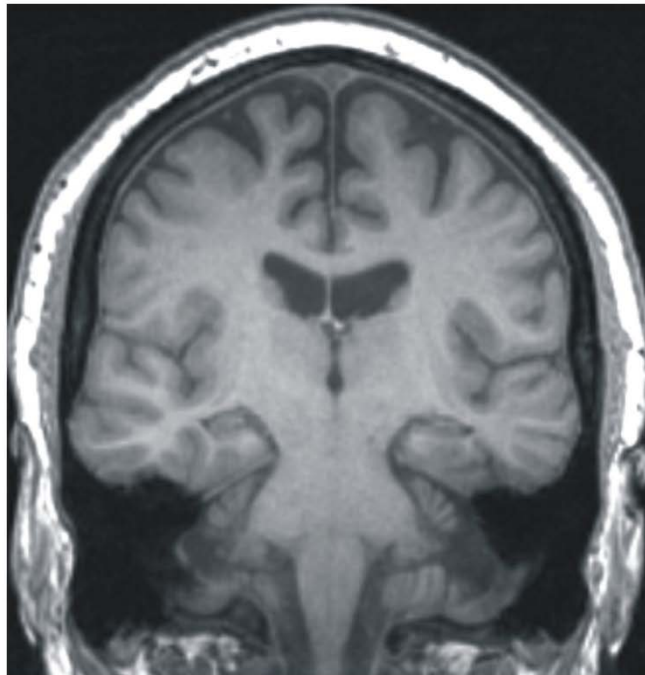
Patient (BHS): TE 015

Figure 4.2. Sample T1-weighted images of epilepsy cohorts: (A) Patient FT026 with left temporal lobe epilepsy determined to be 'MRI-negative' for hippocampal volume reductions and signal abnormalities (LTN) and (B) epilepsy patient TE015 with isolated bilateral hippocampal sclerosis (BHS) and no other apparent structural or signal abnormalities.

4.3.3. Stimuli and Task.

A slightly modified version of the DMS paradigm used in Experiment 1 was used for this study. A number of trials for the configural-relational condition that proved difficult for healthy subjects in Experiment 1 were replaced with a slightly easier version to avoid floor effects in the epilepsy patients. Our first BHS patient tested (LH004) had substantial difficulty remembering task instructions, such as button press assignments, in addition to the requirements of retaining scene stimuli in working memory. Therefore, patients were supported when remembering DMS and control task instructions by presenting instructions for button presses on the lower portion of the display screen (i.e. 'which picture did you just see: 1. Left 2. Right'). No task instructions were present on the screen during delay periods, which was the time-window of analysis for MEG recording (see Chapter 5).

This experiment also included 40 additional configural-relational and non-configural-relational DMS trials in which after the delay period only blank boxes were presented during probe. These 'no probe' trials comprised half of all the DMS blocks and were presented randomly within each block. These trials were used to test later recognition memory (~30-45 minutes after exposure) for the sample stimuli without contamination by repetition effects (for results and discussion see Chapter 6). Apart from these aforementioned modifications, all other stimuli and timing parameters were identical to Experiment 1.

4.4.1. DMS task performance.

As expected, BHS patients were selectively impaired in configural-relational DMS performance. In contrast, the LTN patients with structurally intact hippocampi were unimpaired relative to normal controls (NC) in both the configural-relational, non-configural-relational DMS and control conditions (**Figure 4.3**). A 2x3 repeated-measures ANOVA with condition as the within subjects factor (configural-relational and non-configural-relational DMS) and diagnosis as the between subjects factor (BHS, LTN, NC) revealed main effects for condition ($F(1,19) = 136.19$, $p<0.001$) and group ($F(2,19) = 16.84$, $p<0.001$), as well as a condition by group interaction ($F(2,19)=8.85$, $p<0.005$).

Follow up ANOVAs comparing NC with LTN or NC with BHS confirmed that only BHS differed in the configural-relational DMS performance. This was first determined by a 2x2 repeated-measures ANOVA confirming that the LTN scores were comparable to the NC as a control group in both DMS conditions, with no interaction ($F(1,14)=1.719$, $p=0.211$) or group effects ($F(1,14)=1.77$, $p=0.204$). Then an additional 2x2 repeated-measures ANOVA confirmed an interaction of condition by diagnosis between BHS and NC groups ($F(1,15)=15.61$, $p<0.005$). ANOVAs showed a trend towards an interactions between BHS and LTN performance ($F(1,9)=4.827$, $p=0.056$) and post-hoc independent t-test comparisons (one-tailed, mean, s.e.m.) revealed lower accuracy for the configural-relational DMS condition in BHS patients ($58.0 \pm 5.1\%$) compared to LTN patients ($76.4 \pm 3.2\%$; $t(9) = -2.790$, $p<0.01$). In contrast, no differences were found between groups for non-configural-relational ($t(9)=-1.083$, $p=0.15$) or control ($t(9)=-0.841$, $p=0.21$) condition accuracy, thus confirming a selective impairment within the BHS group for configural-relational working memory performance.

An additional post-hoc paired t-test comparison (one-tailed, mean, s.e.m.), clearly showed lower accuracy in BHS patients for the configural-relational DMS condition ($58.0 \pm 5.2\%$) compared to the control condition ($74.7 \pm 7.6\%$; $t(5) = 2.464$, $p<0.05$) clarifying that this is an effect of memory impairment and not one of difficulties with perceptual discrimination in these patients.
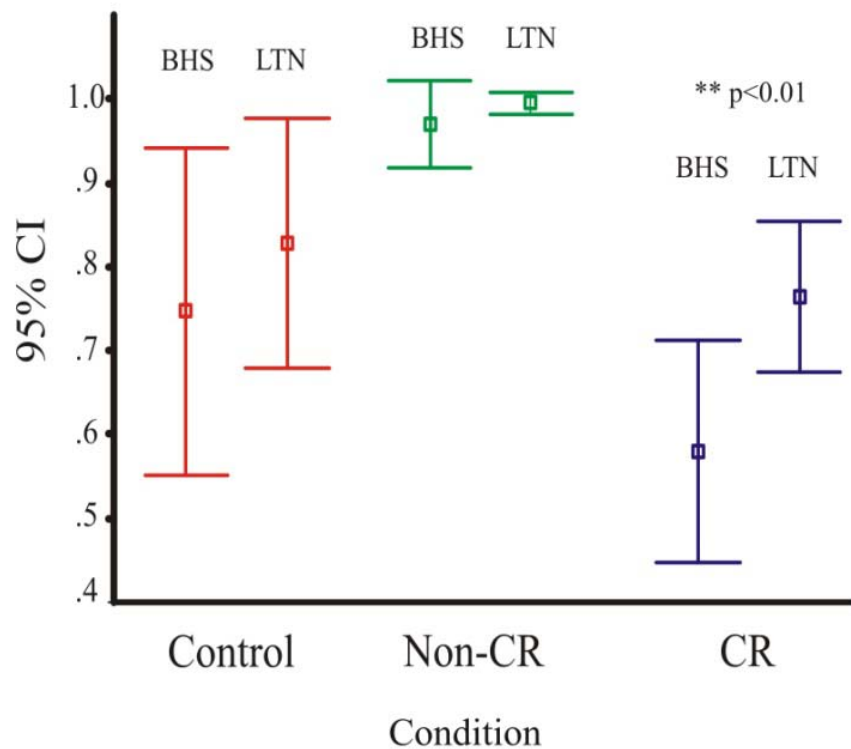
Figure 4.3. Mean behavioural performance in DMS trials in Experiment 3A for bilateral hippocampal sclerosis patients (BHS) and left temporal lobe epilepsy patients determined to be 'MRI-negative' for hippocampal pathology (LTN). The data show a selective impairment for the BHS group for configural-relational (CR) DMS performance (>95% confidence interval; error bars indicate s.e.m.).

4.5. Discussion 3A

In accordance with previous evidence (Hannula et al., 2006; Olson et al., 2006a), epilepsy patients with hippocampal atrophy (BHS) were selectively impaired in their configural-relational working memory performance. While epilepsy patients, matched for the contributing factors of seizures and medications, but normal appearing hippocampi (LTN), displayed no such deficit and in fact, their configural-relational accuracy was comparable to that of normal controls (NC).

Furthermore, there was no difference in non-configural-relational and control condition performance between BHS and LTN patients.

It is important to note, that the involvement of the hippocampus for complex spatial perception/ discrimination in the absence of maintenance requirements still remains an issue to be resolved (Lee and Baxter). However, our current study was not designed to address this issue specifically, but instead aimed to control for such a possibility of perceptual impairments in hippocampally damaged patients when investigating the role of hippocampal integrity in the short-term memory maintenance of configural-relational information. Patients with hippocampal damage (BHS) did show a decrease in control condition performance compared to LTN (**Figure 4.4**), but this decrease was minimal and not significant compared to the drastic configural-relational impairment in BHS patients.

As Lee and Baxter (2010) note, the control condition used in this current study may not provide a sensitive test of the hypothesis that the hippocampus is involved in the perception of spatial stimuli. Hippocampally damaged patients display significant impairments when the view-point of a configural-relational arrangement of a scene is changed, however, these same studies also conclude that this impairment is only consistent across all the hippocampal patients in the test cohort when a delay interval is introduced (Hartley et al., 2007). Arguably, working memory updating could still be required in such tasks, even when no delay period is imposed experimentally, because the online manipulation of a configural-relational arrangement (i.e. mentally rotating the elements of a spatial configuration to a new allocentric representation) requires the active maintenance and the subsequent online manipulation of this information (Hartley et al., 2007).

Our current data rule out the possibility that configural-relational working memory impairments in patients with bilateral hippocampal sclerosis are not due to difficulties in perceptual discrimination as confirmed by the control condition used in this study. Furthermore, our data do not support a role of hippocampal involvement in the perception of spatial stimuli, however, our current study was not designed to investigate this issue systematically. To this end, we do find evidence for a selective impairment in configural-relational working memory that cannot be accounted for by difficulties in perceptual discrimination.

These results suggest that the hippocampus may also be critical to the maintenance of associative visual information of spatial configurations in working

memory. In accordance with this view, a number of imaging studies have shown increased activity in the hippocampus and surrounding medial temporal lobe areas during the delay period of working memory using fMRI (Cabeza et al., 2002; Monk et al., 2002) and using MEG (Campo et al., 2005). Amnesic patients with MTL damage have recently been found to be impaired on other forms of relational visual memory (associative and sequence) and not strictly spatial configurative relations, while their ability to retain items non-associatively is relatively intact (Konkel et al., 2008). Therefore, deficits in the visuo-spatial components of these tasks may be a product of a more generalized impairment in relational binding due to hippocampal damage.

4.6. Summary

We investigated the ability of epilepsy patients with bilateral hippocampal sclerosis (BHS) to retain the configural relationships within natural scenes during working memory delays of 5 seconds (same manipulation of Experiment 1). The strength of this current experiment compared to previous reports (Hannula et al., 2006; Olson et al., 2006a), was the inclusion of a patient 'control' group, as well as normal controls (NC), which consisted of left temporal lobe epilepsy patients without hippocampal damage (LTN) to account for any confounding effects of seizures or medications on working memory performance and MEG recordings (see Chapter 5). With this approach, we identified a selective deficit in configural-relational working memory performance in BHS patients that could not be accounted for by difficulties in perceptual discrimination without delay maintenance (control condition) in these patients. In light of the theta-coupling results of Experiment 1, this selective deficit in configural-relational DMS performance when hippocampal integrity is compromised, proposes a strong link between the hippocampus and occipito-temporal theta synchronization during working memory maintenance of configural relationships. This hypothesis will be directly investigated in Chapter 5.

V. Hippocampus dependent and independent theta networks of active maintenance

Thus far, in a series of working memory experiments using MEG we investigated interareal cortical synchronization within the theta frequency band during the active maintenance of configural-relational or non-configural-relational visual stimuli of working memory delays. Configural-relational maintenance significantly enhanced a theta-coupled network between left fronto-temporal and occipito-temporal sensor groups during delay periods compared to non-configural-relational maintenance in normal controls. Increasing the number of items to be maintained during delays, on the other hand, enhanced bi-frontal theta synchrony. Thus suggesting that the network responsible for the retention of configural relationships is a qualitatively different mechanism than that supporting quantitative increases in the number of discrete stimuli to be maintained. Patients with bilateral hippocampal damage display selective deficits in configural-relational working memory that cannot be attributed to difficulties in perceptual discrimination. Overall, these results suggest that configural-relational delay maintenance recruits a network of synchronous brain regions within the theta band that are functionally different from non-configural-relational and high-load maintenance. The associative and binding properties of the hippocampus commonly described in long term memory may be recruited for this form of working memory in order to maintain the configural relationship of information during delays.

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5.1. Introduction

In accordance with recent evidence (Hannula et al., 2006; Olson et al., 2006a; Olson et al., 2006b; Hartley et al., 2007), we have demonstrated that patients with bilateral lesions in the hippocampus (BHS) are not only impaired in creating new long-term memories, but also display a selective deficit maintaining associative working memory representations of configural-relational information whilst performing normally for non-configural-relational information (Experiment 3A). After a brief presentation of a natural scene, these patients are unable to keep in mind the configural relationship between multiple objects within the scene. Importantly, this selective impairment cannot be attributed to seizure symptoms, medication, or difficulties in perceptual discrimination of visual information.

As discussed in Chapter 2, recent physiological studies in animals raise the possibility that one key functional contribution of the hippocampus towards associative maintenance is to coordinate the persistent activity of cortical representations through hippocampus-dependent theta network oscillations (Buzsaki and Draguhn, 2004; Jones and Wilson, 2005). In humans, we show that actively maintaining a configural-relational representation during working memory delays engages an occipito-temporal and fronto-temporal theta synchronous network (Experiment 1). Furthermore, this network was functionally dissociable from the theta-coupled topography of non-configural-relational forms of working memory even when maintenance demands were quantitatively increased with discrete visual items (Experiment 2).

We therefore propose that configural-relational working memory maintenance is supported by hippocampus-dependent theta oscillations coordinating the synchronized activity of different brain regions that represent the multiple scene elements and their locations in space (O'Keefe and Conway, 1978; O'Keefe, 1993; O'Keefe and Recce, 1993). Although frequently articulated, this link between hippocampal integrity, theta synchrony and associative working memory maintenance has remained largely theoretical (Lisman and Idiart, 1995; Buzsaki and Draguhn, 2004; Montgomery et al., 2008; Sirota et al., 2008). In this chapter, we will directly investigate this possibility, using an integrative approach that combines studying working memory maintenance in bilateral hippocampal sclerosis patients (BHS) who display selective configural-relational DMS task impairments

(Experiment 3A), with the functional measures of theta synchrony as obtained by whole-head MEG recordings.

Experiment 3B. Configural-relational working memory maintenance in BHS

5.2. Aims 3B

Having established that BHS patients are selectively impaired in their ability to maintain the configural-relational aspects of a visual scene (Experiment 3A), we will test our hypothesis that configural-relational maintenance is not only behaviourally, but functionally dependent on hippocampal integrity. Hence, we expect that patients with BHS displaying impaired performance in the configural-relational DMS condition would be accompanied by a selective loss of occipito-temporal theta synchronization. In contrast, non-configural-relational maintenance associated with theta synchrony between frontal and parietal regions will be unaffected by hippocampal injury. Patients with left temporal lobe epilepsy determined to be 'MRI-negative' for hippocampal reductions (LTN), served as a control group to match the effects of recurrent epileptic seizures and antiepileptic medication in BHS patients, but without hippocampal sclerosis.

5.3. Magnetoencephalography Results 3B

5.3.1. Patient groups.

Six patients with temporal lobe epilepsy and Bilateral Hippocampal Sclerosis (BHS) comprised the MEG test group in this study (2 female/ mean age 43.2; SD 9.8). The MEG control group consisted of 6 right-handed patients with left Temporal Lobe Epilepsy (LTN) (2 female/ 37.2; SD 11.4) with normal structural MRI scans (**Figure 4.2**). This LTN group was chosen in order to match the effects of recurrent epileptic seizures and antiepileptic medication of the BHS cohort, whilst comparing structurally intact hippocampi (LTN) to patients with bilateral

hippocampal sclerosis (BHS) (**Table 4.1**). – see Chapter 4 for diagnostic criteria and study modifications.

5.3.2. Theta-Phase coupling results.

To test our hypothesis that hippocampal integrity is necessary for the occipito-temporal theta synchrony of configural working memory, we analyzed LTN and BHS patients' 6Hz phase coupling from similar sensor regions displaying significant synchrony in healthy adults in Experiment 1. Consistent with this hypothesis we expected to find selectively reduced occipito-temporal synchrony for the configural-relational DMS condition in the BHS group while fronto-parietal synchrony would be functionally intact during non-configural-relational DMS.

As expected, the increased occipito-temporal synchrony for configural-relational vs. non-configural-relational conditions was maintained in patients with LTN (**Figure. 5.1A**), but was completely abolished in the BHS group (**Figure. 5.1B**). Direct between group t-test comparisons of configural-relational DMS conditions revealed increased 6Hz synchrony during much of the encoding and delay periods for LTN compared to BHS in the configural-relational condition (**Figure. 5.1C**). Furthermore, within the BHS cohort, t-test comparisons showed the expected preserved increases in fronto-parietal theta coupling for non-configural-relational DMS during maintenance and encoding when compared to the control condition (**Figure. 5.2A**). In fact, t-tests directly comparing configural-relational and non-configural-relational DMS in the BHS group displayed identical time courses of fronto-parietal theta synchrony enhancement (**Figure. 5.2B**). Finally, as in Experiment 1, LTN patients displayed stronger left fronto-temporal synchrony during configural-relational than non-configural-relational maintenance, while BHS patients showed decreased left fronto-temporal synchrony for configural-relational maintenance (**Figure. 5.3**).

A

B
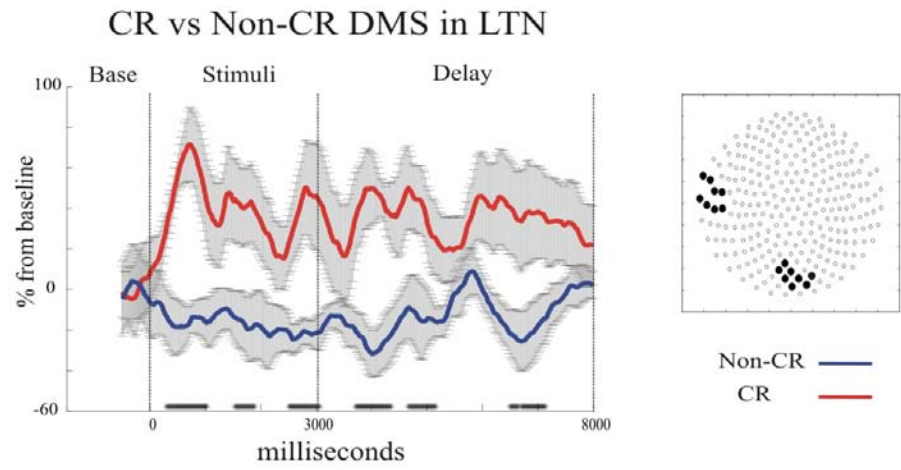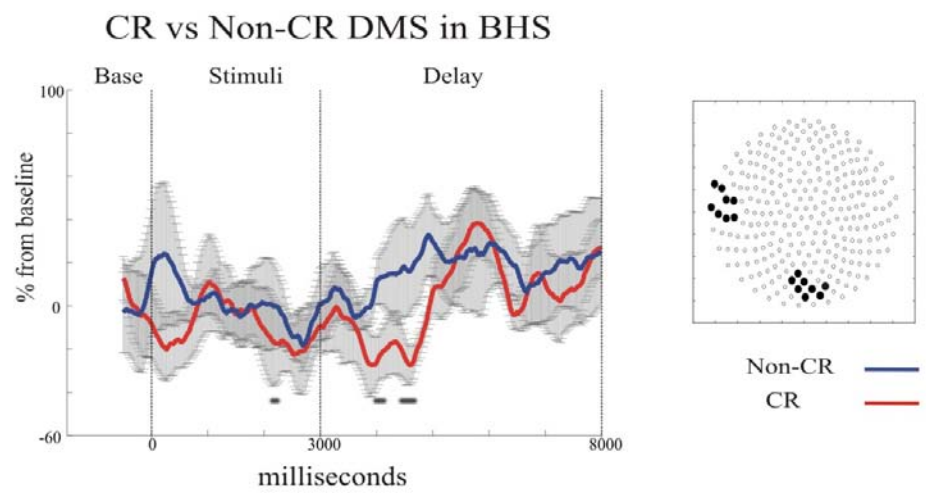
Figure 5.1. Serial measures t-test comparisons of 6 Hz phase-coupling on selected sensor groups (shown on right-side insets) for non-configural-relational (non-CR in blue) vs. configural-relational (CR in red) delayed-match-to-sample (DMS) conditions in Experiment 3B. Increased occipito-temporal theta synchrony for CR DMS during encoding and maintenance was significantly enhanced in temporal lobe epilepsy patients without hippocampal lesions (LTN) (A). This theta synchrony increase was absent for identical sensor groups in bilateral hippocampal sclerosis patients (BHS) during CR DMS (B). In the encoding and maintenance phase of CR DMS, the LTN (blue) group showed stronger occipito-temporal theta synchrony than the BHS group (red) (C).
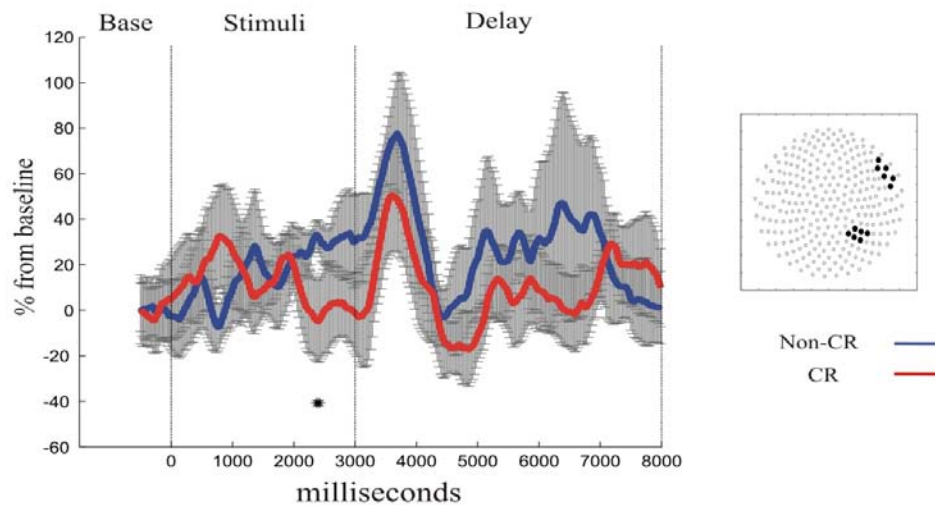
Figure 5.2. Serial measures t-test comparisons of 6 Hz phase-coupling on selected sensor groups (shown on right-side insets) for non-configural-relational (blue) vs. configural-relational (red) delayed-match-to-sample (DMS) conditions in Experiment 3B (threshold of p<0.05 per time point if present continuously over three successive theta cycles indicated by markings on *x*-axis). Theta synchrony of frontal and parietal sensor groups is shown to be intact in bilateral hippocampal sclerosis patients (BHS) during the non-CR DMS condition (A). Comparing non-CR and CR DMS conditions in BHS shows similar spatial-temporal patterns of theta synchrony between frontal and parietal sensor groups (B).
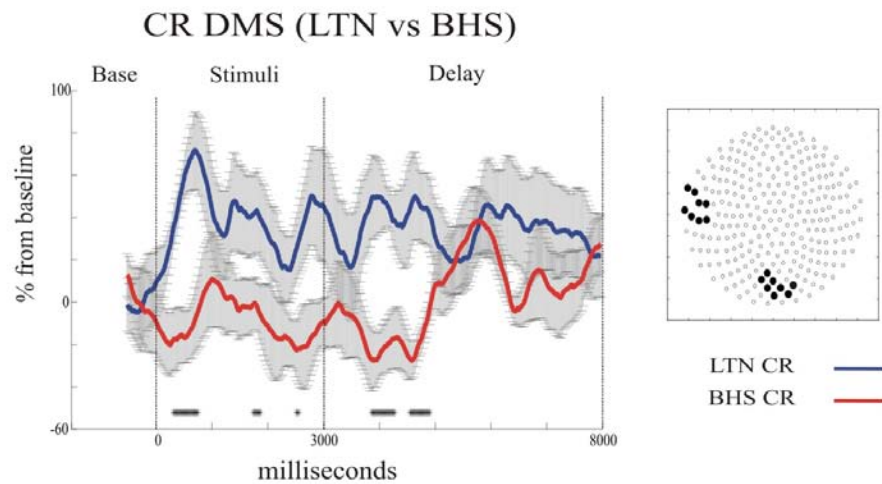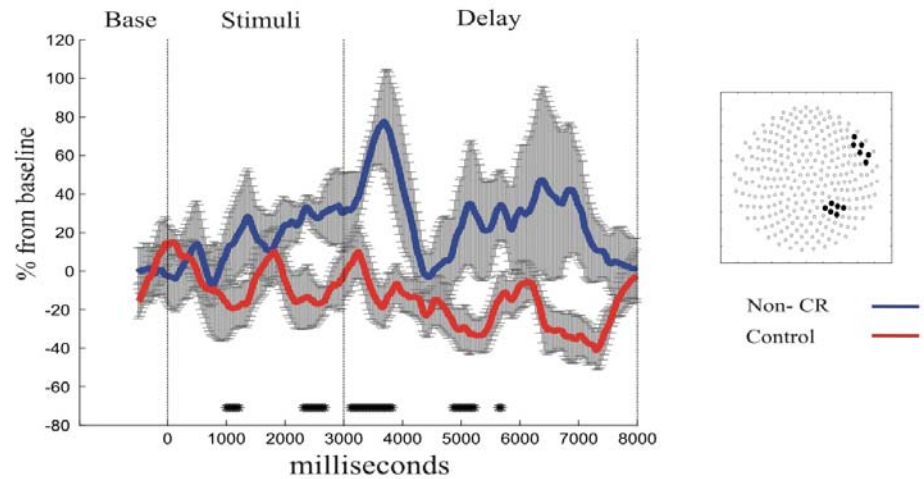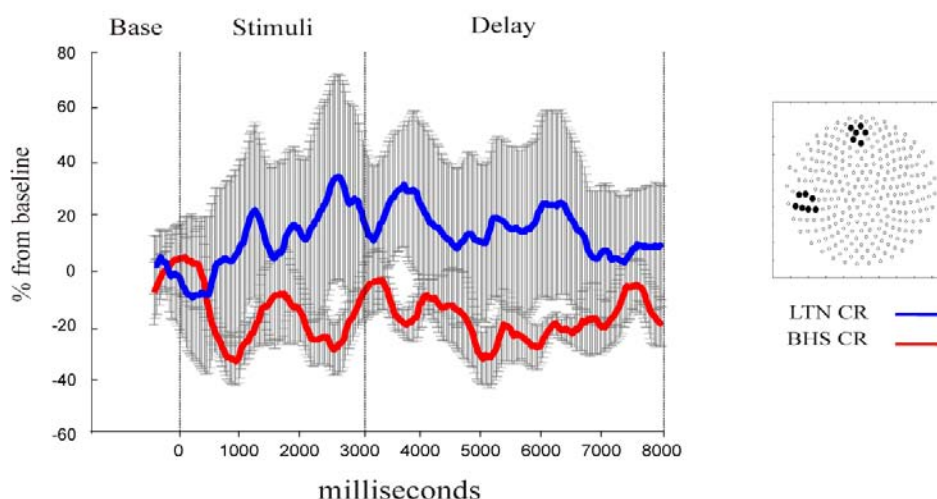
Figure 5.3. Serial measures t-test comparisons of 6 Hz phase-coupling on selected sensor groups (shown on right-side insets) during the configural-relational delayed-match-to-sample (DMS) condition in Experiment 3B. Patients with bilateral hippocampal lesions (BHS shown in blue) display decreased fronto-temporal theta synchrony compared to temporal lobe epilepsy patients without hippocampal lesions (LTN shown in red).

5.4. Discussion 3B

Our findings provide converging evidence for a critical role of hippocampus-dependent cortical theta-synchrony in the active maintenance of configural-relational visual information. We also demonstrate that this theta-synchrony, coupling occipital and temporal sensors, is functionally and anatomically dissociated from non-configural-relational working memory, which engaged theta synchrony between frontal and parietal sensors. Furthermore, Experiment 2 demonstrated that increasing working memory load in the absence of configural-relational maintenance demands engaged bilateral frontal theta-synchrony (**Figure 3.4**). This indicates that occipito-temporal theta synchrony in configural-relational maintenance cannot be accounted for by the additional demands of maintaining more scene elements.

In patients with bilateral hippocampal sclerosis (BHS) occipito-temporal theta synchrony was selectively abolished (**Figure 5.1B**) and also left fronto-temporal

theta synchrony (**Figure 5.3**), while being preserved in our patients with LTN and normal appearing hippocampi (**Figure 5.1A**). Importantly, BHS patients also displayed selective memory impairment in the configural-relational DMS condition while their accuracy for non-configural-relational DMS tasks was comparable to that of healthy control subjects and the LTN group (**Figure 4.4**). Unspecific disease related factors such as seizures, antiepileptic medication and disability which were common to both LTN and BHS groups therefore cannot account for the impairment of the BHS group (**Table 4.1**). This convergence of structural, functional and behavioural results indicates a critical role of hippocampus-dependent theta oscillations in coordinating the active maintenance of configural-relational associations. Previous work has predicted such a possibility (Lisman and Idiart, 1995; Buzsaki and Draguhn, 2004; Ryan and Cohen, 2004; Hannula et al., 2006; Olson et al., 2006a; Olson et al., 2006b; Hannula and Ranganath, 2008; Montgomery et al., 2008; Sirota et al., 2008), but this is the first experiment to combine a functional coupling approach with hippocampal lesion patients necessary to demonstrate this process.

Our findings in the BHS group are consistent with recent behavioural studies that patients with medial temporal lobe amnesia (caused by hypoxic brain injury or encephalitis) have intact working memory performance for object and location, but significant impairments for object-location conjunctions over short delays (Ezzyat and Olson, 2008). Likewise, bilateral hippocampal atrophy caused by hypoxia has recently been reported to cause a selective deficit in configural-relational working memory performance (Hannula et al., 2006).

In light of these results, the hippocampus dependent theta synchronization of occipital and temporal brain regions may contribute to integrating representations of complex conjunctions of scene elements in more rostral portions of the ventral stream, such as the rhinal cortex, with representations of component features in more posterior regions (e.g., visual areas such as V4) (Bussey and Saksida, 2002; Ryan and Cohen, 2004; Aggleton et al., 2007; Hannula and Ranganath, 2008). In mechanistic terms, it has been suggested that through theta oscillations the hippocampus may drive the reciprocal exchange of information with neocortical areas (Sirota et al., 2008). According to this suggestion, the hippocampus may actively control the transfer of neocortical information to the hippocampus itself via theta-phase biasing of neocortical network dynamics (Sirota et al., 2008). With our

findings, one possibility is that the hippocampus drives this reciprocal transfer of information with both occipital and temporal brain regions. Another possibility is that only one of these neocortical regions is entrained by the hippocampus while the other is entrained through cortico-cortical theta synchrony. Both of these possibilities are compatible with our observation that the occipito-temporal theta synchrony is abolished with bilateral hippocampal injury.

In Experiment 1, we showed that the active maintenance of non-configural-relational visual information enhances theta synchrony between right frontal and parietal sensors (**Figure 2.8A),** compatible with earlier studies showing fronto-parietal engagement during working memory (Courtney et al., 1997; Baddeley, 1998; Sarnthein et al., 1998; Postle et al., 2000; von Stein and Sarnthein, 2000; Deiber et al., 2007). In patients with hippocampal atrophy (BHS) this network remained functionally intact (**Figure 5.2A**) and thus independent of hippocampal integrity. This observation of hippocampally independent neocortical theta coupling is physiologically plausible given the evidence for mechanisms responsible for the local neocortical generation of theta oscillations (Blatow et al., 2003). Also, the behavioural functionality of this network was shown to be spared in these patients, as no performance differences for non-configural-relational DMS conditions were found between BHS, LTN, or NC (**Figure 4.4**). Comparisons of configural-relational and non-configural-relational maintenance conditions in the BHS group showed identical time courses of fronto-parietal theta synchrony enhancement (**Figure 5.2B**), suggesting that when hippocampal integrity is compromised, the fronto-parietal theta-network is used also under configural-relational task demands, but this theta-network cannot functionally support the maintenance requirements of configural-relational stimuli.

In Experiment 2, we demonstrated that increasing the number of scene images that had to be retained during the delay from one to five was associated with increased theta coupling of bilateral frontal and temporal sensors (**Figure 3.4B**). This pattern is very similar to increases in frontal theta-coupling during working memory loading tasks found previously in EEG studies (Deiber et al., 2007). Most importantly, the bi-frontal theta synchrony due to increased working memory load was non-overlapping with the occipito-temporal theta-synchrony of configural-relational maintenance (**Figure 2.7B**), indicating that dissociable networks are responsible for supporting the separate maintenance demands of item loading and

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configural-relational representations. This strongly argues against the possibility that functional differences between the configural-relational and non-configural-relational maintenance conditions are due to increases in working memory load in the configural-relational condition. Our current results are compatible with recent studies showing that patients with medial temporal lobe amnesia showed a selective impairment in the ability to maintain relational conjunctions in working memory but had no memory load related impairment (Olson et al., 2006b). This current experiment cannot necessarily rule out the possibility that maintenance under high working memory load may also be compromised by bilateral hippocampal lesions (Fell et al., 2003; Axmacher et al., 2007), however, the high-load working memory performance in the same BHS patients as studied here, will be systematically investigated in Chapter 7.

Enhanced occipito-temporal synchrony in the configural-relational task was initially engaged during encoding and then extended into the delay period for normal controls (**Figure 2.8B**) and patients with LTN and normal hippocampi (**Figure 5.1A**) while in BHS patients, theta synchrony was abolished already during stimulus encoding (**Figure 5.1B**). These findings suggest that bilateral hippocampal injury may impair cooperative binding of information distributed across occipital and temporal regions initially during encoding and the deficits observed during the delay may be an extension of this problem. Such an account is compatible with recent fMRI findings that short-term memory for object-location relationships is accounted for by encoding related activation of the hippocampus (Hannula and Ranganath, 2008).

It should therefore be considered as to whether our data implies a role for the hippocampus also in the perceptual processing of the configural-relational aspects of scenes during encoding (Chalfonte and Johnson, 1996; Graham et al., 2006) -*see discussion* (Shrager et al., 2006). However, such a role of the hippocampus in perceptual feature integration is not supported in our current study because the BHS patients performed normally in the perceptual control condition (**Figure 4.4**) which involved the same amount of visual scene manipulations as in the configural-relational DMS condition - *for similar observations see* (Ryan and Cohen, 2004).

Thus far, we have provided evidence that hippocampus-dependent theta coordination is critical for the ability to maintain configural-relational associative information in working memory. In contrast, non-configural-relational maintenance

was associated with hippocampus-independent theta synchrony between frontal and parietal regions. These data thus show the existence of hippocampus-dependent and hippocampus-independent cortical networks of theta synchronization. Together these results question the long-standing functional and anatomical dichotomy between long-term and short-term memory.

5.5. Supplementary Discussion

A current theoretical assumption of visual working memory maintenance is that the neural patterns involved in stimulus perception may be actively replayed during delays in order to maintain the salient visual properties of the stimulus. As discussed in previous chapters, an influential computational model predicts that the individual features of complex visual stimuli can be represented within the firing patterns of distinct neural assemblies, thus binding these properties into a complete visual perception by the temporal synchronization of these assemblies (Lisman and Idiart, 1995). This model emphasizes the role of theta oscillatory activity within medial temporal lobe (especially hippocampus) as such a clocking mechanism to hold complex perceptual representations "in mind" by the sequenced reactivations of periodically based activity that is phase-coupled to the theta rhythm (Jensen and Lisman, 2005; Jensen, 2006). In light of the results we have shown thus far, recent computational modelling (Lisman and Idiart, 1995; Jensen and Tesche, 2002; Jensen and Lisman, 2005; Jones and Wilson, 2005; Jensen, 2006), and animal single cell recordings (Lengyel et al., 2005) provide strong evidence in favour of theta-phase providing a plausible physiological mechanism for the retention of complex visual information in humans.

A recent study by Fuentamilla and colleagues (2010) applied a multivariate pattern classifier algorithm on time-frequency data obtained from MEG recordings in normal controls while performing the same configural-relational and non-configural relational DMS manipulation as in Experiments 1 and 3. By the use of pattern classifier analysis on time-frequency MEG data, we directly tested whether category-selective neural patterns of activity during visual encoding (indoor or outdoor scene) would be reactivated during the process of image maintenance and whether these category-selective neural patterns were periodically reactivated on a particular theta phase during maintenance (i.e. "nested") – *for methods see* (Fuentemilla et al.).

Consistent with this aim, Fuentamilla and colleagues found a high degree of accurate category-specific reactivations during the delay period, possibly reflecting the 'neural code' attributed to these internally represented stimulus types (**Figure 5.4**). Both non-configural-relational and configural-relational maintenance periods showed a greater amount of reactivations as compared to those obtained during the delay period of the control condition where no working memory maintenance was required. Furthermore, configural-relational maintenance revealed a higher number of accurate reactivations during delays compared to the non-configural-relational condition, supporting evidence from previous chapters (Experiments 1-3) that maintaining the configural relationship of visual scenes within working memory is more demanding upon network maintenance.
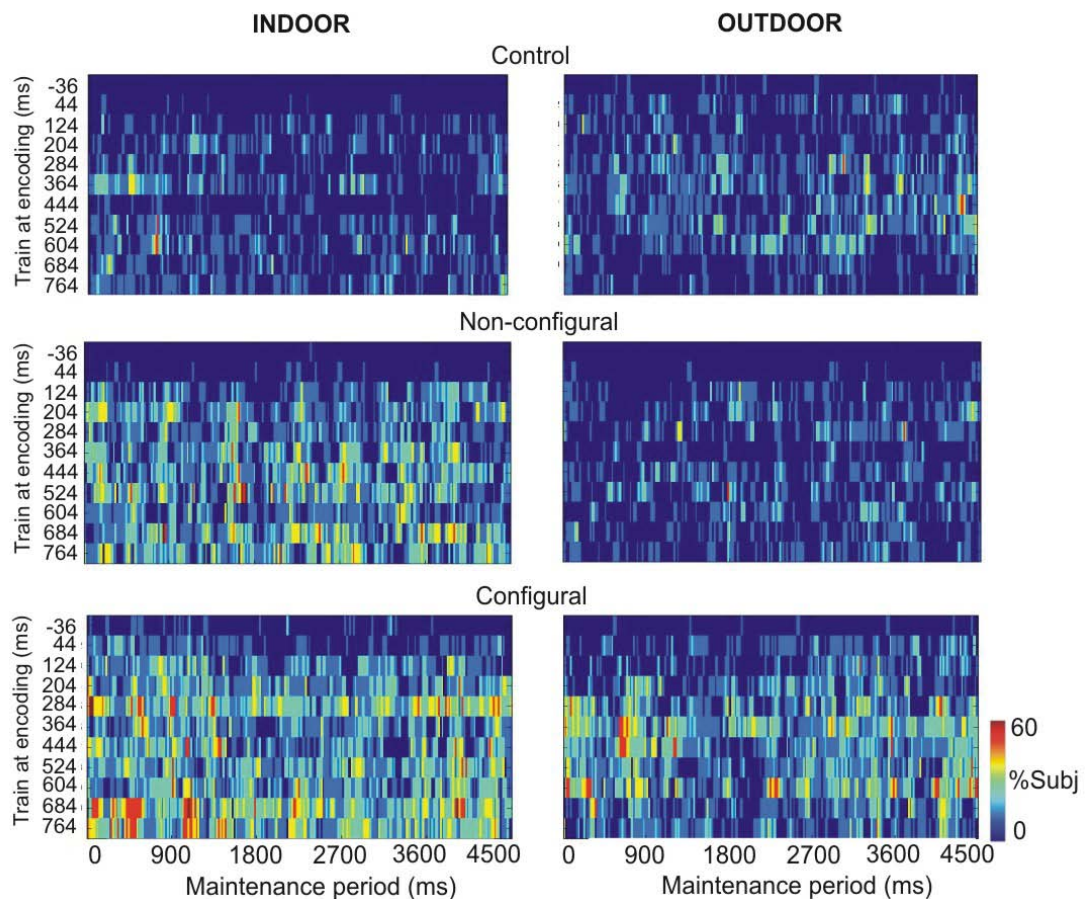
Figure 5.4. Specific-category stimuli reactivation during the maintenance period (4.5 sec, *y*-axis) for each DMS condition (same design as Experiments 1 and 3) and for each trained classifier (*x*-axis). Plots represent the percentage of subjects that showed significant reactivations.

In Experiments 1 and 3, we demonstrated characteristic theta-coupled networks supporting configural-relational and non-configural-relational forms of working memory maintenance. Next, Fuentamilla and colleagues tested if these MVPC feature reactivations during maintenance were phase-locked to the ongoing theta networks similar to those found in Experiments 1 and 3. Since a detailed time course estimation of category specific reactivation was obtained, all of the theta phases that coincided with a significant reactivation predicted by all classifiers could be calculated with a corresponding "Phase-Locking Value" (PLV) (Lachaux et al., 1999) as a measure of the resulting sensor-by-sensor theta phase concentration during delays (6Hz – same frequency band as Experiments 1-3). Consistent with the hypothesis that the neural code of information maintenance would be actively clocked by a corresponding theta phase (Jensen and Lisman, 2005), significant PLV was found for both non-configural-relational and configural-relational stimuli reactivations during working memory maintenance (**Figure 5.5B**). In accordance with the results of Experiments 1 and 3, category-selective reactivations tended to be engaged in distinct regional sensor space. While non-configural-relational neural pattern reactivation was linked to fronto-parietal regions, configural-relational information maintenance was coupled to theta phase activity from fronto-temporal regions (**Figure 5.5A**).
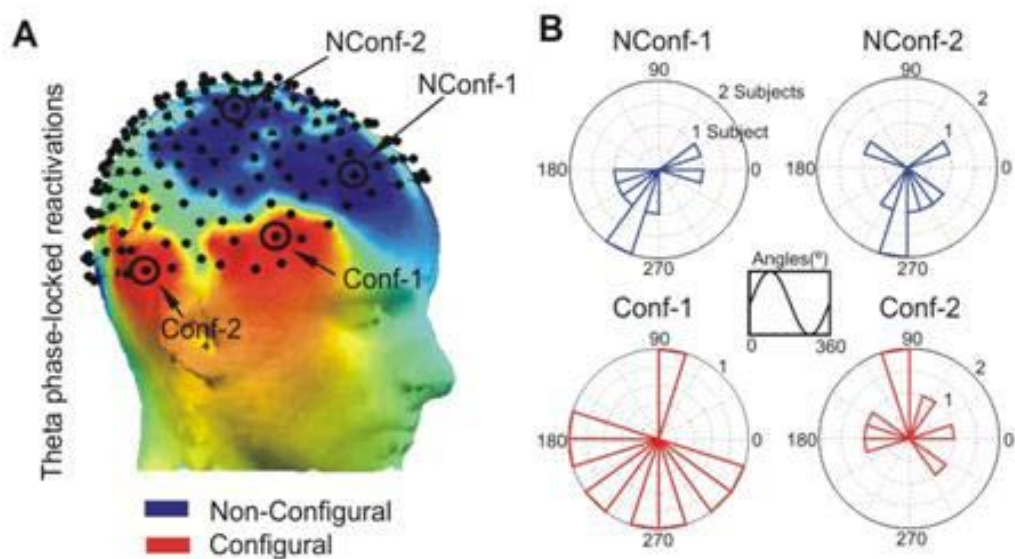
Figure 5.5. Theta (6Hz) phase coupling of category specific reactivation during configural-relational and non-configural-relational maintenance (same design as Experiments 1 & 3. (A) Sensor-specific significant (*P*<0.05) theta phase-locking reactivations for non-configural-relational and configural-relational information. For each experimental condition and for each subject, sensor-by-sensor phase-locking was obtained by collecting theta phase state that corresponded to each time-point where any of the 10 classifiers predicted indoor/outdoor reactivation during delay. Once a global "Phase-Locking Value" (PLV) was obtained for each sensor, an exclusive conjunction analysis was computed where non-configural-relational and configural-relational PLV was compared to the control condition PLV. Those sensors that showed significant PLV (two-sample *t*-test; *P*<0.05) were plotted in the scalp surface. (B) Specific subject angle distribution at two selected sensors from (A).

Fuentamilla and colleagues demonstrated for the first time, non-invasively and in humans, direct evidence for the theoretical prediction that neural patterns of stimuli during encoding are internally reactivated during maintenance when stimuli are no longer present externally in the environment. Additionally, that these working memory reactivations are supported by an ongoing theta rhythm that is phase-locked to the stimulus attributes being maintained in Experiments 1 and 3. These results critically support the computational model predicting that complex visual features are periodically reactivated over delays and that these reactivations are nested on a particular theta phase in humans during working memory (Lisman and Idiart, 1995; Jensen and Lisman, 2005; Jensen, 2006). This work supports previous electro-physiological observations in the visual cortex of non-human animals (Lee et al., 2005b) and within the fronto-hippocampal circuitry (Siapas et al., 2005). It has been suggested that this mechanism of phase-coupling may be a basis for the ability to actively maintain multiple items during working memory delays (Lisman and Idiart, 1995). Furthermore, these results support the hypothesis proposed in earlier chapters that configural-relational and non-configural-relational forms of information processing and maintenance seem to rely on dissociable theta networks.

5.6. Summary

Thus far, in a series of working memory experiments using MEG we investigated cortical synchronization within the theta band during the active maintenance of configural-relational or non-configural-relational visual stimuli using DMS tasks in healthy adults and patients with bilateral hippocampal lesions (Chapters 2-5). Using this approach, we show that actively maintaining configural-relational aspects of a visual scene was associated with theta oscillatory coupling of temporal and occipital visual areas (Chapter 2) and furthermore, that this theta-network is critically dependent on the integrity of the hippocampus. The ability to support configural-relational forms of working memory are behaviourally show to depend on hippocampal integrity and cannot be explained by difficulties in perceptual integration (Chapter 4). In contrast, non-configural-relational maintenance was associated with theta synchrony between frontal and parietal regions (Chapter 2) and this form of maintenance was unaffected by hippocampal injury. Work by Fuentamilla and colleagues, demonstrates that the periodic reactivation of configural-relational and non-configural-relational information during the working memory maintenance period of the same experimental manipulation is locked to the on-going theta synchronization of these networks (Fuentamilla et al., 2010). Together, these data indicate that hippocampus-dependent theta synchrony plays an anatomically specific and critical role in for the active maintenance of configural-relational information.

VI. Interactions of long term and short term memory

Working memory processes have been thought to be anatomically and functionally distinct from the networks necessary for the encoding and retrieval of long-term memory. Thus far we have provided convincing evidence that hippocampus dependent theta synchronization is necessary for certain forms of short-term working memory maintenance and thereby challenging this classical distinction. This evidence supports the notion of functional and anatomical interactions between working memory maintenance and long-term memory encoding. In this chapter we will explore how configural-relational and non-configural-relational maintenance processes interact with long-term retention and elucidate the commonalities of these memory networks.

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6.1. Introduction

Some early models saw of working memory as a gateway through which information could enter into long-term memory (Atkinson and Shiffrin, 1971). However, this view was later abandoned because of the strong evidence of double dissociations between these processes (see Chapter 1). Recently, some influential models of working memory (Baddeley, 1998, 2003; Axmacher et al., 2007) have begun to regain the possibility that what is rehearsed or maintained in working memory can update and interact with representations in long-term memory. Recent electrophysiological studies in patients with hippocampal damage (Axmacher et al., 2009) and genetic models in rodents (Malleret et al.) have supported such interactions where long-term and short-term memory processes compete for common resource allocation. This notion is supported by our results showing that long-term memory regions are critical to certain forms of short-term maintenance, however, the question still remains: Does hippocampal involvement in the working memory maintenance of configural relationships represent a genuine working memory process that is separable from long-term declarative memory?

Experiment 3C. Delayed recognition memory after configural-relational DMS in epilepsy and normal controls

6.2. Aim 3C

We have demonstrated that the hippocampus is necessary for the retention of configural relationships of visual information during working memory. Furthermore, that configural-relational maintenance is supported by hippocampal-dependent theta synchronization of occipito-temporal and fronto-temporal regions during delay periods. This network has been shown to be dissociable from non-configural-relational forms of working memory that function independently of the hippocampus. The medial temporal lobe, and specifically the hippocampus, are pivotal to the encoding and retrieval of long-term memory. We therefore, investigate in this section if hippocampal recruitment during configural-relational working

memory maintenance results in long-term retention of stimuli compared to non-configural-relational maintenance.

6.3. Study Design 3C

6.3.1. Participants.

This experiment was an extension of experiment 3A & 3B. For demographics and DMS behavioural performance of epilepsy patients and normal control participants see Experiment 3A, Chapter 4. For MEG recording analysis and discussion see Experiment 3B, Chapter 5.

6.3.2. Stimuli and Task.

As previously described in Chapter 4, a slightly modified version of the DMS paradigm implemented in Experiment 1 was used for this study (Experiment 3). One modification made in this experiment was the inclusion of 40 additional configural-relational and non-configural-relational DMS trials in which after the delay period only blank boxes were presented during probe. These 'no probe' trials comprised half of all the DMS blocks and were presented randomly within each block. These trials were used to test later recognition memory for the sample stimuli without contamination by repetition effects (**Figure 6.1**).

Approximately 30-40 minutes after completing the DMS tasks, participants took a recognition memory test. For this test, subjects were shown images of which 40 were samples in the configural-relational task (no probe trials) and 40 samples in the non-configural-relational task (no probe trials), and 80 were new scenes (foils) which we not presented previously in the experiment. The scenes were presented one every three seconds with a 1 sec inter-trial-interval where participants classified the scenes as 'old' or 'new' by making one of two button presses. They were instructed that accuracy and reaction times were equally important.
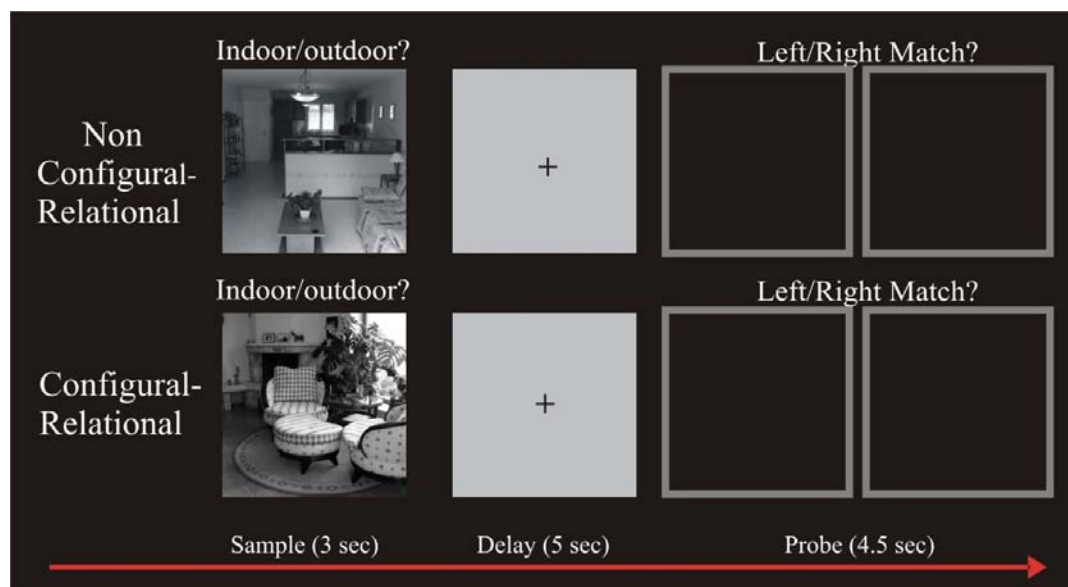
Figure 6.1 Example of modifications made to DMS paradigm design for Experiment 3C, where sample images were later used for long-term memory recognition tests from 'no probe' non-configural-relational (top) and 'no probe' configural-relational (bottom) DMS trials.

6.4. Results_3C

6.4.1. Delayed recognition performance.

When analyzing participants' delayed recognition memory performance we calculated a measure of 'corrected hit-rate' for each participant to adjust for any response bias at probe (see Chapter 1 for discussion). This was done by taking the number of 'hits' – subject responds 'yes' to a previously seen target stimuli, subtracted by the number of 'false alarms' – subject responds 'yes' to a previously unseen foil stimuli; then divided by the total number of trials. This results in a single value for each participant, ranging from 0 to 1, adjusted for an individual's bias for recognition memory responses between target and probe stimuli.

Using corrected hit-rate, we found that both NC and LTN participants displayed increased delayed memory recognition for configural-relational stimuli compared to the non-configural-relational DMS condition, while this was not the case for BHS patients (**Figure. 6.2**). A 2x3 repeated-measures ANOVA of corrected recognition (hit) rates with condition (configural-relational and non-configural-relational samples) as the within-subjects factor and group (LTN, NC, BHS) as the

between-subjects factor, revealed main effects for condition ($F_{(1,20)}=9.26$, $p<0.01$) and group ($F_{(2,20)}=7.92$, $p<0.005$), as well as, a group by condition interaction ($F_{(2,20)}=3.55$, $p<0.05$). Compared to LTN, BHS patients were impaired in both recognition memory tests (main effect of group, $F_{(1, 10)} =5.26$, $p<0.05$). Post-hoc paired t-test comparisons (one-tailed, mean, s.d.) showed increased delayed memory recognition for configural-relational stimuli compared to non-configural-relational stimuli for the NC (0.54 ± 0.20 vs. 0.36 ± 0.13, $t(10) = -3.65$, $p<0.01$) and for the LTN (0.370 ± 0.07 vs. 0.310 ± 0.05, $t(5)=-1.974$, $p=0.05$) but not for the BHS (0.19 ± 0.11 vs. 0.17 ± 0.08, $t(5)=-0.484$, $p=0.649$) group (- see **Table. 6.1,** for raw DMS and delayed recognition raw scores).
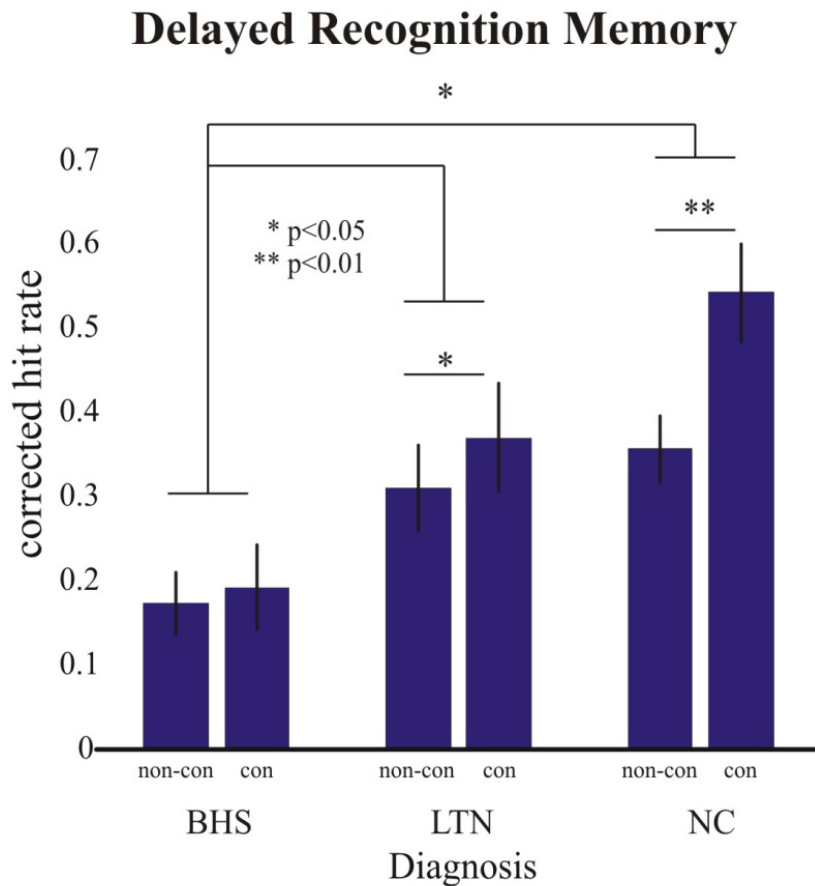
Figure 6.2. Mean corrected hit rates of delayed recognition memory for non-configural-relational (non-CR) and configural-relational (CR) stimuli in experiment 3C for patients with bilateral hippocampal sclerosis (BHS), left temporal lobe epilepsy patients determined to be 'MRI-negative' for hippocampal reductions (LTN), and college-aged normal controls (NC). P-values denoting differences between conditions are indicated by asterisks (paired t-test, one-tailed, s.d.).

Subject	Dx	non-configural	configural	Recog_non-configural	Recog_configural
DH006	BHS	0.975	0.5484	0.2273	0.1717
EM011	BHS	1	0.75	0.3109	0.4135
GP013	BHS	0.9744	0.4118	0.0731	0.1282
TC016	BHS	1	0.6216	0.1133	0.2448
TE015	BHS	0.8718	0.675	0.2016	0.0817
m_r	BHS	1	0.475	0.1123	0.1123
SC005	LTN	1	0.775	0.4721	0.5971
RG014	LTN	1	0.65	0.3003	0.2746
SN010	LTN	*	*	0.2026	0.2688
FT026	LTN	1	0.7692	0.4125	0.5494
h_p	LTN	1	0.85	0.1375	0.2375
NM021	LTN	0.975	0.775	0.332	0.2949
DB	NC	1	0.85	0.3	0.625
GS	NC	0.975	0.875	0.3375	0.7875
JL	NC	1	0.925	0.4125	0.8375
SD	NC	1	0.9	0.5875	0.7125
YA	NC	1	0.775	0.325	0.475
SR	NC	1	0.7368	0.2539	0.1974
YH	NC	0.975	0.825	0.5375	0.5875
VA	NC	0.975	0.875	0.2375	0.5125
SA	NC	1	0.7895	0.4375	0.5375
AB	NC	1	0.675	0.1315	0.3468
DB2	NC	1	0.7692	0.3614	0.3473

Table 6.1 Raw accuracy scores for bilateral hippocampal sclerosis patients (BHS), left temporal lobe epilepsy patients determined to be 'MRI-negative' for hippocampal reductions (LTN), and normal controls (NC) on configural-relational (CR) and non-configural-relational (non-CR) DMS tasks and corrected hit-rates of delayed recognition test. * Due to a hardware malfunction no behavioural data was collected for SN010 during MEG recording.

6.5. Interim Discussion 3C

In this section we aimed to investigate the relationship between working memory maintenance and long-term memory by testing memory for scene images (for those trials that had no probe images) from each DMS condition in a delayed recognition memory test. The DMS samples maintained previously during the MEG session in patients (BHS & LTN) or during a behavioural session in normal controls (NC) had to then be discriminated from previously unseen novel scenes 30-45 minutes later. It is important to note, that the encoding and maintenance period of

configural-relational and non-configural-relational DMS tasks used in this experiment had identical task instructions and stimuli characteristics. On all trials, participants were asked to make a deep encoding judgment ('indoor or outdoor picture?') during the encoding period and the only factor that can attribute to delayed-recognition memory differences between conditions are the innate encoding and maintenance requirements of the tasks.

In normal controls and LTN patients, delayed recognition memory for scenes from the configural-relational DMS trials were significantly better than for scenes from the non-configural-relational DMS trials (**Figure 6.2**). Importantly, delayed recognition memory for both types of samples was at chance in patients with BHS, despite the fact that these patients were unimpaired in the working memory performance for non-configural-relational stimuli (**Figure 4.4**), as well as, displayed intact fronto-parietal synchrony (**Figure 5.2A**). These findings suggest that the hippocampus-dependent theta coordination of occipital and temporal regions during configural-relational maintenance also contributed to encoding into long-term memory but this was not the case for the hippocampus-independent fronto-parietal theta synchrony.

These results are compatible with the suggestion that hippocampal maintenance operations may contribute to long term memory encoding (Ryan and Cohen, 2004; Ezzyat and Olson, 2008; Hannula and Ranganath, 2008). This possibility of a link between hippocampus-dependent theta network contributions to working memory maintenance and encoding into long-term memory will be further investigated in subsequent sections. In contrast to long-term memory, working memory is defined as a transient process (Mishkin and Delacour, 1975; Baddeley, 1984), where stimulus retention will decay over time and the maintenance of these representations are susceptible to delay interference (Shrager et al., 2006; Shrager et al., 2008). Next we will investigate these two notions of working memory in the configural-relational and non-configural-relational DMS tasks used in Experiments 1-3.

Experiment 4. Configural-relational and 5-item load DMS with variable delay length.

6.6. Aim_4

Working memory has been described as a transient process, where information held activity in mind will degradate over time. However, the temporal distinctions between what is considered short-term working memory maintenance and long-term memory consolidation are not well defined. Evidence from earlier chapters demonstrating engagement of long-term memory regions of the medial temporal lobe during configural-relational maintenance further obfuscate the temporal distinctions between what constitutes long-term memory and short-term working memory. In this section we will briefly explore variations of DMS memory performance during delay length manipulations of configural-relational and high load non-configural-relational maintenance.

6.7. Study Design_4

6.7.1. Participants.

Twenty one right-handed healthy subjects (7 male/ mean age 24.5, SD 5.3 years) participated in the experiment. All participants were recruited from the University College of London's Psychology departmental subject pool and were determined to have no extraneous neurological or psychological disorders that would confound our results. In addition, all subjects displayed normal or corrected to normal visual acuity. All participants gave written informed consent to participate and the study was approved by the guidelines of the ethics committee of the University of London Research Ethics Committee for human-based research. All participants were compensated at a rate of £6 per hour for the entirety of the study, which averaged two hours to complete.

6.7.2. Stimuli and task design.

This experiment was a modified version of the configural-relational condition of Experiment 1 and the high-load condition of Experiment 2 where the DMS delay period length was manipulated. Participants were required to retain visual information from the sample scenes over a delay period of either 5 seconds (same as Experiments 1, 2 & 3), 15, or 30 seconds in order to make a correct answer at probe.

In the 5-item load condition, subjects were instructed to maintain the 5 sample stimuli over a randomized delay period of either 5, 15, or 30 seconds whilst fixating on a cross. At probe subjects were presented with a single picture (1 sec) and asked to indicate if the picture was a "match" or "non-match" to one of the aforementioned sample stimuli. Targets and foils were randomized and counterbalanced across testing blocks. After which, there was a 3.5 sec inter-trial-interval where subjects were instructed to blink before fixing on the next cue (0.5 sec).

In the configural-relational condition, an indoor or an outdoor scene was presented for 3 sec. This was followed by a blank screen with a fixation cross with a randomized delay period of either 5, 15, or 30 seconds followed by two test stimuli for 4.5 seconds. The two test stimuli were manipulated versions of the scenes involved changes in the relations among some elements of the scenes. Participants were required to encode and maintain the configural relationships of the objects within the scene in order to make a correct answer at probe. (-see Experiment 1-Chapter 2, for full methods and design description).

All stimuli, task parameters, and timing (except delay lengths) were identical to Experiment 1 (configural-relational condition) and Experiment 2 (5 item 'load' condition). Conditions were presented in blocks and order of the testing blocks were randomized for each subject to avoid any practice effects for conditions (2 blocks of 30 trials for each condition).

6.8.1. DMS performance.

A 2x3 repeated-measures ANOVA (condition x delay length) revealed a main effect for DMS condition on participants' accuracy (F (1, 19) = 4.44; p = 0.048) and a trend for delay length (F (2, 38) = 2.82; p = 0.072). An interaction of DMS condition by delay length approached significance (F (2, 38) = 3.07; p =0.058). However, pair-wise comparisons (two-tailed, mean, s.e.m.) within DMS conditions displayed significant decreases in accuracy when visual stimuli were maintained for 5 seconds compared to 30 seconds in the high-load condition (87.3 ± 1.76% and 81.3 ± 2.4%, respectively; t(19) = 3.04, p = 0.007), but no accuracy decrease was found in the configural-relational condition (5 seconds, 81.3 ± 2.2% and 30 seconds, 82.3 ± 1.7%; t(19) = -0.42, p = 0.677). - **Figure 6.3**
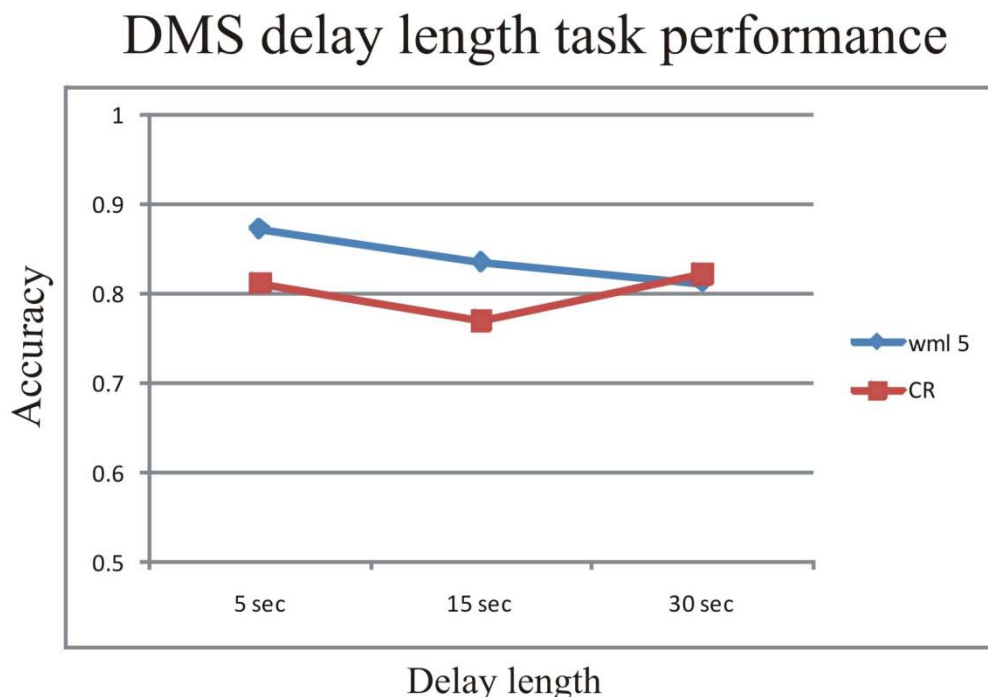
Figure 6.3. DMS task performance with variable delay lengths of 5, 15, or 30 seconds for the configural-relational condition; similar to Experiments 1 & 3 (red) and the 5 item 'load' condition; similar to Experiment 2 (blue). High working memory load accuracy significantly decreases (p = 0.007) when maintenance requirements are extended from 5 to 30 seconds while configural-relational performance remains relatively constant for maintenance periods up to 30 seconds long.

6.9. Interim Discussion 4

In previous chapters we demonstrated that configural-relational maintenance engages a functionally dissociable theta-network than high load working memory maintenance. The current results of Experiment 4 suggest that the maintenance requirements of these networks are differentially effected by the temporal demands of delay length. Decreases in DMS performance when maintenance requirements are extended to 30 seconds in the high load condition are suggestive that the quantitative representation of multiple scenes are susceptible to working memory decay/noise within this short temporal window (i.e. 5 to 30 seconds of maintenance). However, DMS performance supporting the qualitative representation of the configural relationships within a scene remained relatively constant within this time frame.

Furthermore, Experiment 3C above, showed a clear enhancement of delayed-recognition memory for configural-relational stimuli up to 45 minutes after initial exposure when hippocampal integrity was intact. Together these results suggest that hippocampal theta recruitment during configural-relational maintenance may result in the simultaneous encoding of sample stimuli within the brief temporal window characteristic of working memory delays and this retention may persist up to 45 minutes later (i.e. long-term recognition memory).

It is important to note that at the shortest delay length (5 seconds), high load DMS performance was considerably higher than configural-relational DMS accuracy (see **Figure 6.3**). Then with increases in delay length, high load DMS performance steadily decreased to that of the configural-relational condition irrespective of maintenance length. It is thereby possible that after 30 seconds of maintenance both of these conditions may display similar profiles of declining DMS accuracy merely because performance was not initially matched at 5 seconds. Testing longer manipulations of delay length between conditions would help to elucidate this issue, however, doing so would result in very lengthy experiments and is beyond the scope of this current work. However, using manipulations of delay length as a method of increasing demands upon maintenance of high load working memory processes will be further explored in Experiment 7 of the following chapter.

Experiment 5. Delay interference during configural-relational and 5-item load DMS

6.10. Aim 5

In Chapter 4, we demonstrated that the hippocampus is necessary to support short-term working memory for configural relationships (Experiment 3A). Retention of this information seems to not decay as quickly as 5-item maintenance over delay intervals up to 30 seconds long, even if short delay performance (~5 seconds) is lower than that of high-load DMS tasks (Experiment 4). Furthermore, maintenance of configural relationships results in long-term retention of stimuli (~45 minutes) compared to non-configural-relational forms of information (Experiment 3C). It is therefore, important to determine if hippocampal-dependant configural-relational DMS performance is in fact a working memory process that is dissociable from long-term memory encoding. It has recently been argued that a hallmark of working memory is its susceptibility to interference during delay periods and furthermore, that the hippocampus is not critical for this form of active maintenance or working memory (Shrager et al., 2006). In this section we will investigate delay interference susceptibility of configural-relational and high load non-configural-relational DMS task performance.

6.11. Study Design 5

6.11.1. Participants.

17 right-handed healthy subjects (11 Male/6 Female, mean age 24.5 yrs/ SD ± 4.78 yrs) participated in the experiment. All participants were recruited from the University College of London's Psychology departmental subject pool and were determined to have no extraneous neurological or psychological disorders that would confound our results. In addition, all subjects displayed normal or corrected to normal visual acuity. All participants gave written informed consent to participate and the study was approved by the guidelines of the ethics committee of the University of London Research Ethics Committee for human-based research. All

participants were compensated at a rate of £6 per hour for the entirety of the study, which averaged two hours to complete.

6.11.2. Stimuli and Task Design.

The experiment consisted of two blocked delayed-match-to-sample (DMS) working memory conditions, the configural-relational condition and a high-load (5-item) non-configural-relational condition. Participants were required to maintain either 5 scenes (same as the 5-item working memory load condition of Experiment 2) or the configural relationships within a single scene (same as the configural-relational DMS condition in Experiments 1 and 3) over a 5 seconds delay period. Experimental parameters, response requirements and stimulus material were the same as in the original experiments (- see Chapters 2 & 3). There were two blocks of 30 trials each, resulting in 60 trials per DMS condition (ordering of block presentation was randomized).
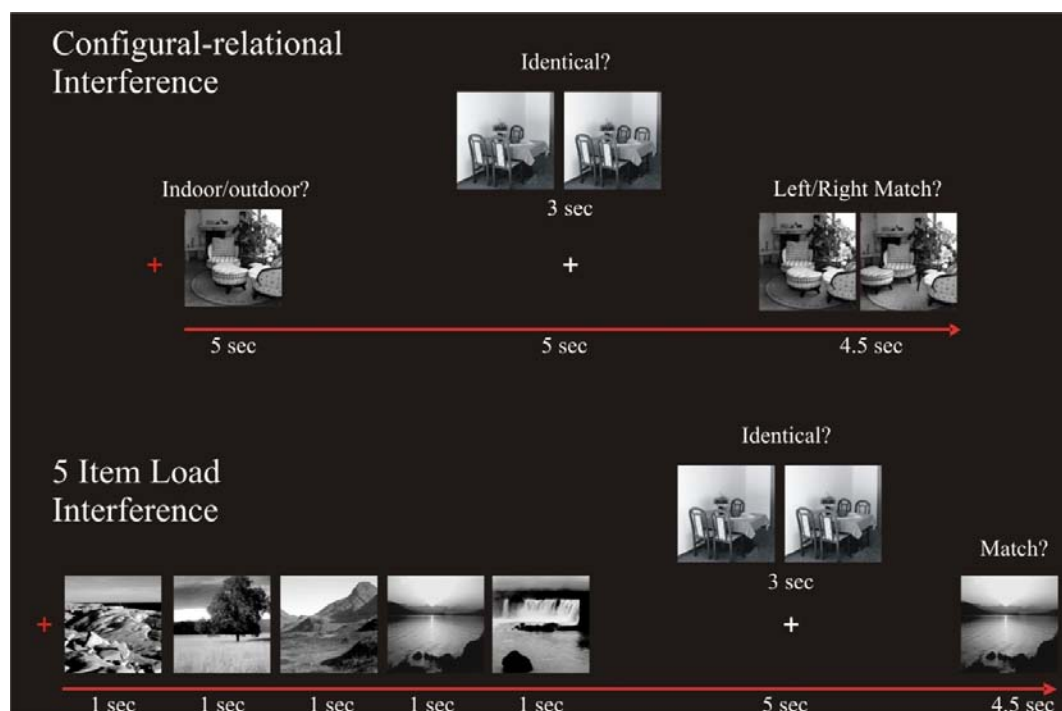

Figure 6.4. Examples of a configural-relational interference trial (top) and a high-load non-configural-relational interference trial (bottom) used in Experiment 5. Participants were required to maintain either 5 scenes (same as the 5-item working memory load condition of experiment 2) or the configural relationships within a single scene (same as the configural-relational DMS

condition in experiments 1 and 3). Interference trials required participants to make a 'same/different' perceptual discrimination judgment during delay maintenance (same as probe during control conditions of experiments 1 & 3).

In the 5 item working memory load condition, subjects were instructed to maintain 5 sample stimuli (1 sec each) over a 5 sec delay period whilst fixating on a cross. At probe subjects were presented with a single picture (4.5 sec) and asked to indicate by button press using the index or middle finger of the right hand if the picture was a "match" or "non-match" to one of the aforementioned sample stimuli. Targets and foils were randomized and counterbalanced across testing blocks. After which, there was a 2 sec inter-trial-interval where subjects were instructed to blink before fixing on the next cue (0.5 sec). The configural-relational DMS condition stimulus timing was exactly matched to the configural-relational condition in Experiments 1 and 3.

To investigate the effect of interference on the maintenance process for these DMS conditions we presented a difficult visual discrimination task for 3 seconds during the middle of the 5 second delay period on 50% of the DMS trials. The interference tasks required participants to judge if two scenes presented side-by-side were the same or different (same task as the control condition probes in Experiments 1 and 3). This interference task was chosen to disrupt 'visual' rehearsal (or replay) by introducing a task that is relevant to the current working memory maintenance demands (i.e. indoor and outdoor natural scenes).

6.12. Results 5

6.12.1. Behavioural performance.

A 2x2 within-subjects ANOVA (condition x interference) on the 17 participants tested revealed main effects for condition ($F(1,16) = 7.477$; $p = 0.015$) and for interference ($F(1,16) = 22.535$; $p = 0.0001$) with no interaction ($F(1,16) = 2.212$; $p = 0.156$). Accuracy was significantly decreased in both DMS conditions when the interference task was presented during delay periods. The 5-item load DMS condition performance (83.00 % ± 2.45%) was significantly reduced when the interference task was introduced during the delay period (76.24% ± 3.03%, $t(16)=2.439$, $p = 0.027$). Similarly, the configural-relational DMS condition

performance (78.71% ± 2.47%) significantly decreased with the interference task (67.18% ± 2.38%, t(16)=5.229, p=0.0001).

5-item WML and CR with interference task
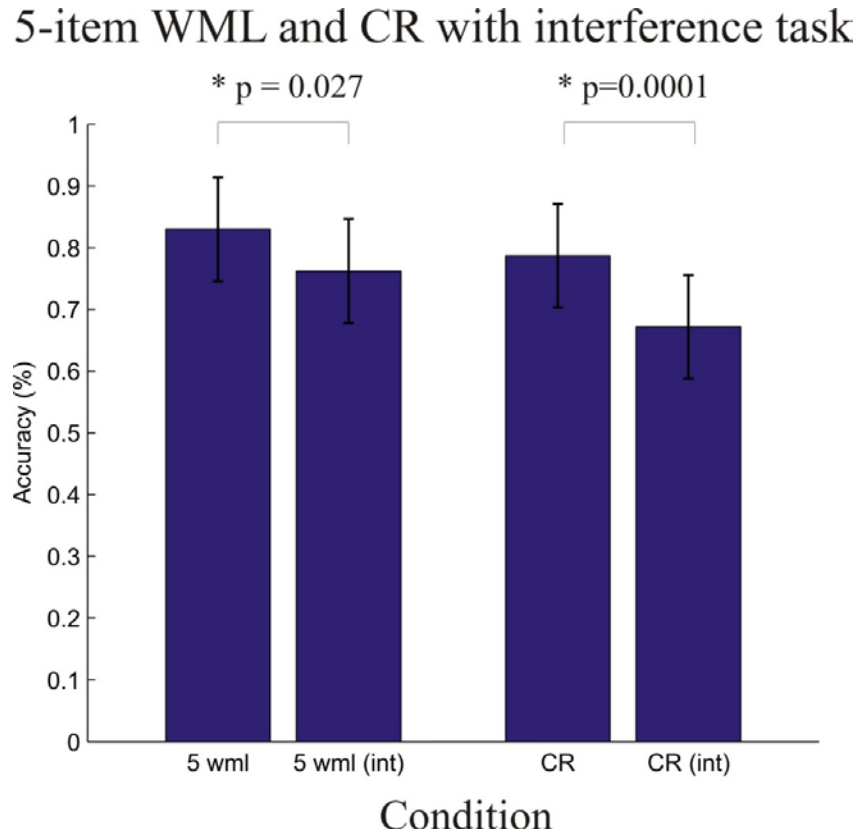
Figure 6.5. Mean behavioural performance of non-configural-relational 5-item working memory load DMS condition (5 wml) and the configural-relational condition (CR). Performance of both conditions were significantly reduced by delay interference (int) of perceptual discrimination judgments presented during a delay period of 5 seconds.

Importantly, no differences were found in the performance of the interference task between DMS conditions (5-item load DMS interference task (73.00% ± 2.17%) and configural-relational DMS interference task (71.00% ± 2.89%, t(16)=0.619, p=0.545) suggesting that the delay maintenance processed were specifically disrupted and that decreases in performance were not attributed to additional difficulties in encoding sample stimuli between conditions (**Figure 6.6**). The impairment of DMS performance with task interference during the delay indicates that the configural-relational DMS task, as well as the high load DMS condition both required an active maintenance processes akin to working memory (Shrager et al., 2006; Shrager et al., 2008).
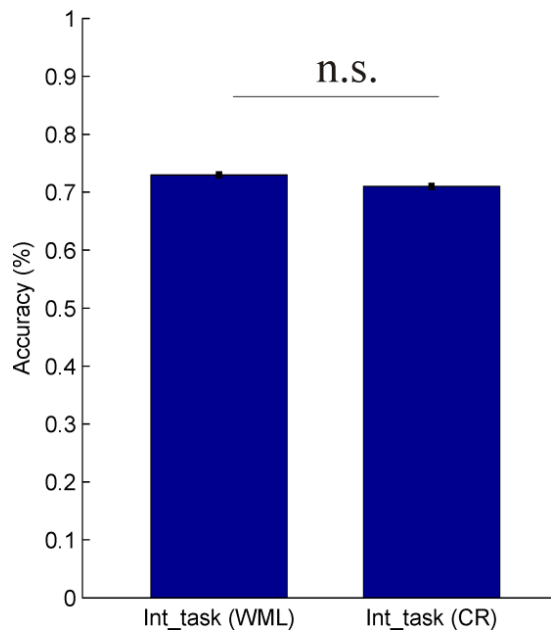
Figure 6.6. Mean behavioural performance of the interference task (int_task) for the 5-item working memory load DMS (WML) and the configural-relational DMS (CR) conditions. No differences between participants ability to perceptually discriminate between visual scenes (int_task) suggests that the delay maintenance processed were specifically disrupted in this manipulation and that decreases in performance (Figure 6.5) were not attributed to additional difficulties in encoding sample stimuli between conditions.

6.13. Interim Discussion 5

It has recently been argued that a hallmark of working memory is its susceptibility to interference during delay periods (Shrager et al., 2006; Shrager et al., 2008) and furthermore, that the hippocampus is not critical for this form of active maintenance or working memory. In Experiment 5, we clearly demonstrate that not just the high working memory load condition, but also the configural-relational condition of our DMS task was shown to be sensitive to delay interference supporting the possibility raised by our theta-coupling data that the configural-relational condition also required an active form of maintenance akin to working memory (Experiments 1 & 3). Our findings therefore show that the hippocampus is

functionally and behaviourally critical for actively maintaining the configural relationships of visual stimuli in working memory. In agreement with other authors - *for review see* (Ranganath and Blumenfeld, 2005), our data call for a reconsideration of the classical distinction between hippocampus-dependent long-term memory and hippocampus-independent active maintenance of working memory.

6.14. Final Discussion

Hippocampal involvement during maintenance of configural relationships seems to share characteristics of working memory processes and long-term declarative memory. We demonstrate that configural-relational short-term delay maintenance results in increased long-term recognition memory compared to non-configural-relational stimuli (Experiment 3C). This is despite lower working memory performance on these tasks compared to non-configural-relational stimuli prior to delayed recognition memory testing (Experiment 3A). This is presumably due to hippocampal recruitment via theta phase-coupling to support this form of working memory maintenance will enhance subsequent long-term encoding of this information. It seems likely that this enhancement is due to differences in the active maintenance of configural-relational and non-configural-relational stimuli since the task requirements both required the same deep-encoding judgment (i.e. indoor/outdoor scene). Furthermore, non-configural-relational maintenance was shown to decay over DMS delays of 30 seconds while configural-relational performance was relatively unchanged.

Similar results have shown that short-term persistence of information within working memory can enhance long-term retention of the same information (Schon et al 2004; Ranganath et al, 2005; Khader et al., 2007) suggesting a common resource allocation for both stimulus maintenance and encoding. In accordance with this view, the opposite effect has also been shown, where incompatible or faulty representations held in working memory can also interfere with long-term memory recognition (Axmacher et al., ; Axmacher et al., 2009).

It has recently been argued that the key hallmark of working memory is its susceptibility to interference during delay periods (Shrager et al., 2008), in which long-term memory is resilient. Under this assumption, a recent behavioural study

has shown that hippocampal damaged patients only display short-term memory deficits under conditions where individuals with normal hippocampi are not susceptible to delay interference (i.e. stimulus retention relies on long-term memory - (Shrager et al., 2006; Shrager et al., 2008).

Contrary to this, we show that task-relevant interference presented during short-term retention intervals (5 seconds) can disrupt configural-relational working memory maintenance to the same degree as high item load working memory of similar stimuli (Experiment 5). Furthermore, we demonstrated that increases in working memory load is characterized by the functional theta synchronization of bi-frontal cortical regions (Experiment 2) and was completely non-overlapping with the occipito-temporal synchrony of configural-relational working memory maintenance (Experiment 1). Thus, engagement of the hippocampus during configural-relational delay maintenance (Experiment 3B) is not merely a compensatory mechanism to quantitatively enhance capacity, but instead is necessary to coordinate the qualitative binding of these associative representations during working memory.

Together, these findings challenge the classical functional-anatomical distinctions between long and short-term memory. We have demonstrated that hippocampus-dependent theta coordination is critical for the ability to maintain configural-relational information in visual working memory, yet will also result in long-term persistence of this information. Furthermore, this process is susceptible to interference during delay periods akin to working memory processes. These studies shed light on the functional relationships between the neural systems necessary for short-term maintenance and long-term retention, yet the nature of how these processes can interact with one another will be the focus of Chapter 7.

6.15. Summary

In this chapter we have provided evidence of behavioural interactions between short-term working memory maintenance and long-term memory retention. Hippocampus-dependent configural-relational maintenance results in increased delayed recognition, while this enhancement does not occur for non-configural-relational working memory (Experiment 3C). Furthermore, retention of non-configural-relational multi-item representations seem to decay over delays of 30 seconds while persistence of the configural relationships within a scene seem to be relatively unaffected within this same time-window (Experiment 4). However, both of these forms of delay maintenance are susceptible to interference during short-term retention periods characteristic of working memory processes (Experiment 5). These results elucidate an interactive relationship between these processes and demand reconsideration of the classical functional-anatomical distinctions between long and short-term memory.

VII. Distraction can improve Memory

The ability to maintain transient information actively in our mind can become disrupted by external distraction. This short-term working memory maintenance has been shown to compliment long-term memory encoding and retention, thus sharing common resource allocations. However, in cases when stimulus maintenance is faulty, distraction interference could then alternatively allow a more accurate memory representation to persist that does not rely on working memory resources. In this section we will demonstrate that disruption of working memory maintenance by task-irrelevant distraction can abolish deficits in delayed memory retention in patients with Bilateral Hippocampus Sclerosis. Likewise, under similar conditions where healthy participants' working memory performance becomes compromised, we show that disruption of this faulty maintenance will lead to improvements of memory performance over retention intervals.

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Working memory is the ability to maintain information actively in the mind over short periods of time and has been thought to provide an interface between long-term memory and perception (Baddeley, 2003). This short-term persistence of information within working memory has been shown to enhance long-term retention of the same information (Experiment 3C – *also see* Schon et al, 2004; Ranganath et al, 2005; Khader et al., 2007) suggesting a common resource allocation for both stimulus maintenance and encoding. In accordance with this view, incompatible or faulty representations held in working memory have been shown to interfere with long-term memory recognition (Axmacher et al., 2009, 2010). Recent genetic models in rodents have shown that mice with a mutant expression reducing hippocampal long-term synaptic potentiation (a proposed neural mechanism for long-term memory encoding) results in increases working memory capacity (Mallerat et al., 2010). These results suggest that the opposite interaction might be possible as well, where disrupting working memory maintenance could allow for alternative long-term memory processes to overcome stimulus recognition during retention intervals. In such cases where working memory performance is impaired, maintenance disruption could lead to improvements in delayed recognition memory performance due to the persistence of an alternate and possibly more accurate memory signal.

Experiment 6. Working memory load and task-irrelevant delay distraction in epilepsy

7.2. Aim 6

It has been recently proposed that when the number of items to be held in working memory (load) exceeds the maintenance capacity of working memory resources then long-term memory systems are recruited in order to compensate (Fell et al., 2003; Rissman et al., 2008; Shrager et al., 2008). Under this assumption, information incapable of persisting in the transient capacity-limited system of working memory is transferred to a more robust long-term memory store, and thereby preserving a dichotomy between these two systems. Many studies of patients

with medial temporal lobe amnesia have reported selective impairments in the ability to maintain the relational conjunctions in working memory, but no memory load related impairment (Olsen et al., 2006; Finke et al., 2008). While others have found working memory load impairments in amnesic patients (Shrager et al., 2006; Shrager et al., 2008). This calls into question if deficits found in patients with Bilateral Hippocampal Sclerosis (BHS) for configural-relational DMS tasks (Experiment 3A) are due to impairments of supporting increases of the quantitative elements to be maintained within a scene or the qualitative relational binding of this information. This interpretation seems unlikely, since the occipito-temporal theta-coupling found during configural-relational maintenance in normal controls (Experiment 1) and the epilepsy control group (LTN – Experiment 3C), was non-overlapping with theta-coupling bi-frontal sensor topography of high load working memory maintenance (Experiment 2). In this section we will test the same BHS group as in Experiment 3 on their ability to retain increases in the number of individual scene elements (i.e. working memory load – Experiment 2) over delays of 5 seconds and furthermore, determine the susceptibility of DMS performance to task-irrelevant delay distraction.

7.3. Study Design_6

7.3.1. Patient groups.

All patients underwent comprehensive clinical whole brain MRI scans including: T1-weighted, proton density, T2-weighted and FLAIR acquisition protocols. These images were reviewed by two experienced consultant neuroradiologists who found no structural abnormalities other than bilateral hippocampal sclerosis in the BHS group. All patients were attending clinics at the Department of Clinical and Experimental Epilepsy of UCL Institute of Neurology and the National Hospital for Neurology and Neurosurgery.

BHS: 5 right-handed patients with temporal lobe epilepsy and Bilateral Hippocampal Sclerosis (BHS) (2 female/ mean age 43.2±10.9 yrs) participated in the experiment as the testing group (same cohort as Experiment 3 – Chapters 4 & 5)

TLE: 6 right-handed patients with temporal lobe epilepsy (1 female/ 36.7±12.4 yrs) determined to be 'MRI-negative' for hippocampal volume reductions and signal abnormalities (TLE), served as a control group to match the effects of recurrent epileptic seizures and antiepileptic medication in BHS patients, but without hippocampal sclerosis. We were only able to recruit three of the six same LTN patients from Experiment 3 as many had subsequently under gone temporal lobe resection in hopes to alleviate seizures. Therefore, three additional right hemisphere dominate TLE patients with no hippocampal reductions were included in this study. The TLE control group was well balanced with 3 left and 3 right hemisphere dominate temporal lobe epilepsy patients with normal hippocampi (- see results section displaying no behavioural differences between right and left dominate TLE patients on the DMS tasks tested in this experiment).

Normal Controls: In addition, 15 normal controls (NC) participated in the same experimental paradigm (9 female/mean age 24.7±3.9). Magnetoencephalography Recordings were collected on 10 of these participants while undergoing the experimental procedure (Experiment 2).

7.3.2. Stimuli and Task.

We tested the same epilepsy patients with bilateral hippocampal sclerosis (BHS) as in Experiment 3 on their ability to actively maintain multiple visual scenes within working memory over a brief delay period (same design as Experiment 2). Using a delayed-match-to-sample task (DMS), patients were presented a series of black and white pictures of natural scenes (1, 3, or 5 images presented serially) and asked to keep all of these pictures actively in their mind. After a delay period of 5 seconds, we presented a single picture that was from the prior stimulus array or was a completely novel scene (**Figure 7.1A**). Patients were then asked to indicate if they had seen the picture previously or if it was entirely new. We additionally tested a group of patients with temporal lobe epilepsy (TLE) determined to be 'MRI-negative' for hippocampal reductions to control for the effects of recurrent epileptic seizures and antiepileptic medication in BHS patients, but without hippocampal atrophy.
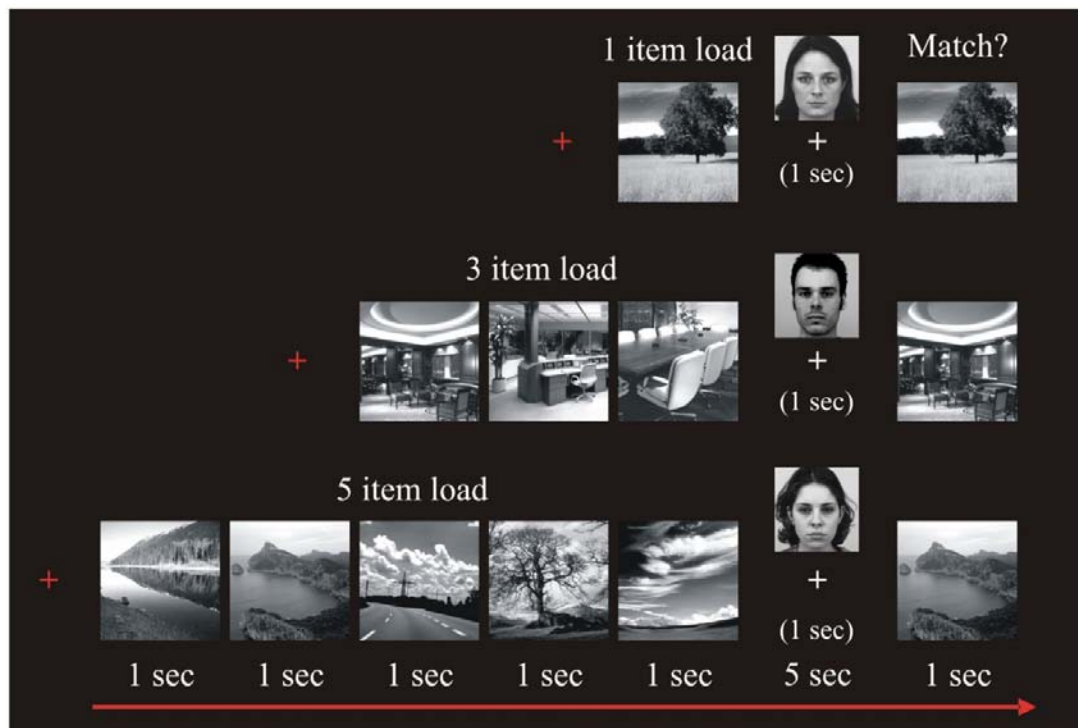
Figure 7.1. Working memory 'load' DMS paradigm. An example of delayed match to sample trials where 1 item load (top), 3 item load (middle), or 5 item load (bottom) presented serially must be maintained over a 5 second delay period in order to make a "match" decision at test. On 50% of trials a face distracter is presented for 1 second. – same as Experiment 2.

With this design we also sought to disrupt active maintenance of scenes by task-irrelevant distraction during the delay period. Distracter stimuli consisted of 105 black and white photographs of male and female faces with neutral emotional expression selected from the Karolinska Directed Emotional Faces database (Lundqvist et al., 1998). On half of the DMS trials, a face distracter stimuli (1 sec) was presented during the delay period (jittered within a 3 sec window during the middle of the delay).

7.4.1. DMS task performance.

Since the control patient group in this study consisted of 3 left and 3 right temporal lobe dominate epilepsy patients (TLE) without hippocampal atrophy, we first analyzed DMS performance between the left and right dominate TLE patients to determine if they could be characterized behaviourally as a homogenous comparison to BHS patients. A 2x3 repeated-measures ANOVA (distracter x load) confirmed main effects for Load ($F_{(2,8)} = 9.31$; p=0.008) and as expected not for Distracter ($F_{(1,4)} = 0.081$; p=0.790). The between subjects comparison (Right TLE and Left TLE), confirmed no differences ($F_{(1,4)} = 0.485$; p = 0.525) and no interaction with distracter susceptibility by group (p=0.680). Therefore, we are confident that left and right dominate TLE patients can be merged as a homogenous patient control group to compare to BHS patients.

A 2x3x3 repeated-measures ANOVA with load (1,3,5 item) and distraction (with or without) as the within-subjects factor and group (BHS, TLE, NC) as the between subjects factor revealed main effects for load ($F_{(2,26)} = 54.70$; p = 0.0001), for group ($F_{(2,23)} = 4.85$; p = 0.017), and a strong trend for distraction ($F_{(1,23)} = 3.69$; p = 0.067). Furthermore, we revealed a distraction by group interaction ($F_{(2, 23)} = 4.18$; p = 0.028) and a nearly significant load by group interaction ($F_{(3.7,43.0)} = 2.55$; p = 0.56). Post-hoc Tukey HSD tests revealed pair-wise mean differences between the BHS and the NC groups at the 0.05 level.

Follow up repeated-measures ANOVAs directly comparing the BHS and NC groups revealed main effects for load ($F_{(2,36)} = 45.84$; p =0.0001), for distraction ($F_{(1,18)} = 7.19$; p = 0.015), and for group ($F_{(1,18)} = 16.95$; p = 0.001). Also, a load by group ($F_{(1.8,33.1)}=4.25$; p=0.025), distraction by group ($F_{(1,18)}=14.12$; p=0.001 and a load by distraction by group ($F_{(1.37, 24.6)}=3.98$; p = 0.046) interaction. Post-hoc One-way ANOVAS confirmed that BHS patients were significantly impaired for 1 item (BHS ($90.8 \pm 3.11\%$) vs. NC ($97.0 \pm 4.26\%$) p=0.008), 3 item (BHS ($67.8 \pm 12.7\%$) vs. NC ($91.0 \pm 6.01\%$) p=0.0001), and 5 item (BHS ($70.0 \pm 7.64\%$) vs. NC ($81.0 \pm 7.53\%$) p = 0.012) DMS loading when compared to the NC group (**Figure 7.3**). When distraction was presented during the delay, BHS performance increased enough to absolve all group differences (p>0.05).

Furthermore, follow up ANOVAs comparing only the patient groups' accuracy for 3 and 5-item loading (with/without distraction) revealed a main effect for distraction ($F(1,9) = 6.57$; $p = 0.031$) and a clear trend of a distraction by group interaction ($F(1,9) = 4.27$; $p = 0.069$) (**Figure 7.2**).
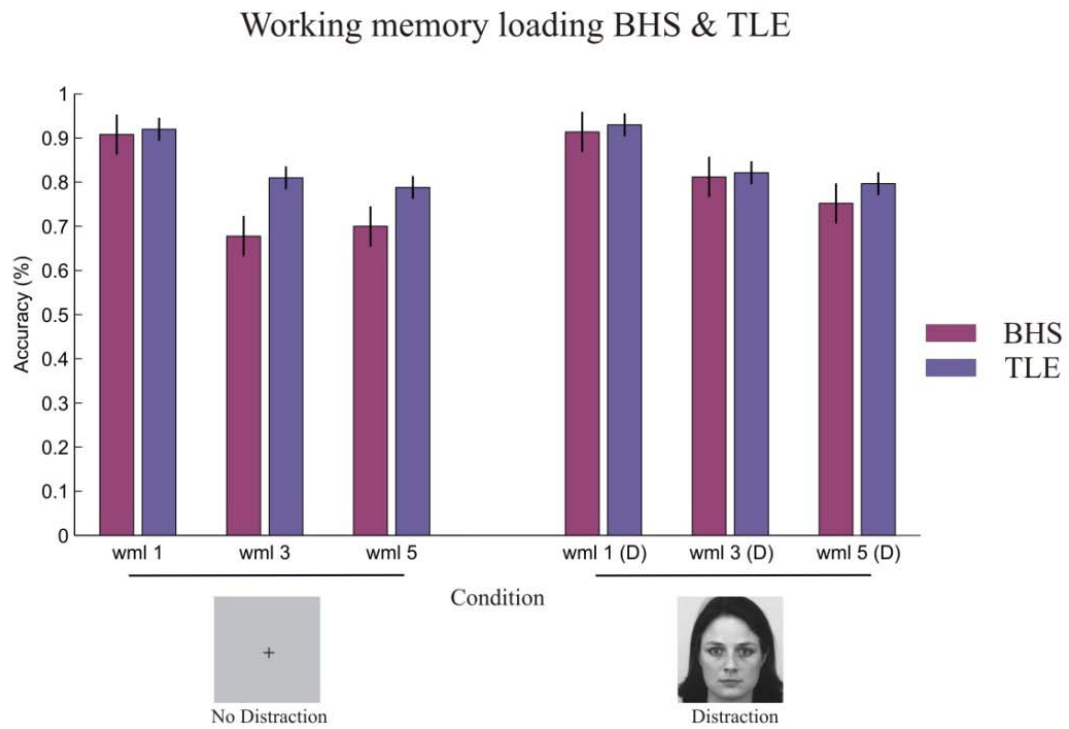
Figure 7.2. Mean DMS accuracy for patients with bilateral hippocampal sclerosis (BHS, in purple) and temporal lobe epilepsy but no hippocampal damage (TLE, in blue) when required to maintain 1, 3 , or 5 scenes (wml) over a 5 second delay period. When no distraction was present during the retention period (left) BHS patients' high-load performance was decreased compared to TLE patients, however, when a task-irrelevant face distraction was presented for 1 sec during delays (wml D), BHS high-load DMS performance was enhanced.
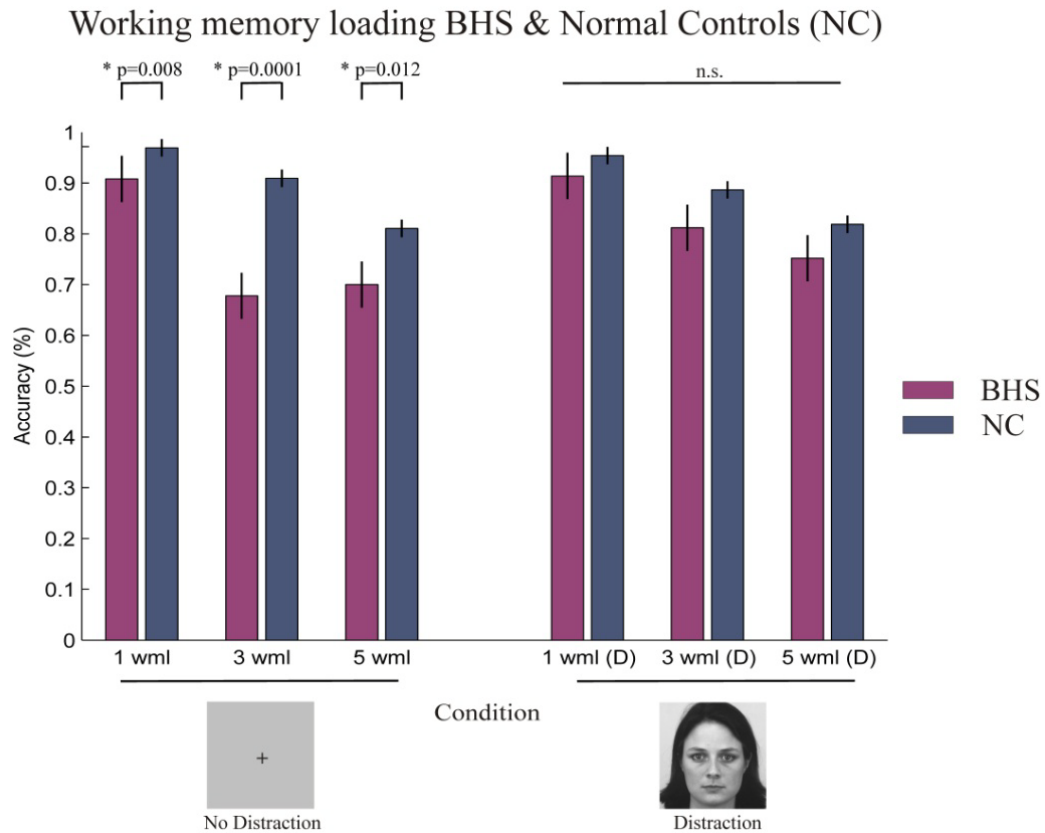
Figure 7.3. Mean DMS accuracy for patients with bilateral hippocampal sclerosis (BHS, in purple) and young normal control participants (NC, in grey) when required to maintain 1, 3 , or 5 scenes (wml) over a 5 second delay period. When no distraction was present during the retention period (left) BHS patients' performance was significantly compared to NC, however, when a task-irrelevant face distraction was presented for 1 sec during delays (wml D), BHS high-load DMS performance was enhanced to the level of young NC.

| Subject	Dx	Wml 1	Wml 3	Wml 5	Wml 1 (D)	Wml 3 (D)	Wml 5 (D)
DH006	BHS	0.94	0.81	0.76	0.97	0.94	0.91
EM011	BHS	0.94	0.71	0.60	0.91	0.78	0.68
GP013	BHS	0.90	0.78	0.79	0.88	0.82	0.80
M_R	BHS	0.87	0.56	0.69	0.88	0.74	0.63
TE015	BHS	0.89	0.53	0.66	0.93	0.78	0.74
SN010	L_TLE	0.94	0.66	0.63	0.79	0.62	0.76
FT026	L_TLE	0.97	0.88	0.91	0.97	0.97	0.88
NM021	L_TLE	1.0	0.97	0.94	1.0	1.0	0.86
G_C	R_TLE	0.97	0.89	0.83	1.0	0.97	0.74
J_F	R_TLE	0.96	0.76	0.85	0.91	0.74	0.68
R_C	R_TLE	0.68	0.70	0.56	0.91	0.63	0.86

Table 7.1. Raw scores for working memory load (and task-irrelevant distraction) DMS tasks in patients with bilateral hippocampal sclerosis (BHS) and temporal lobe epilepsy (TLE) without hippocampal atrophy.

7.5. Interim Discussion 6

When BHS patients were required to actively maintain more than one image in their mind, performance quickly decreased when compared to the TLE control group (**Figure 7.2**), however, in the absence of hippocampal reductions (TLE), patients' ability to maintain multiple items within working memory does not differ from college age normal controls (NC). This suggests that the hippocampus may contribute to some compensatory mechanisms of multi-item working memory maintenance. However, it is important to note the decreases in 3 and 5 –item load DMS performance in BHS (**Figure 7.2**) are not nearly as profound as the configural-relational DMS impairments for BHS patients compared to temporal lobe epilepsy patients without hippocampal damage (**Figure 4.4**). It is therefore likely that hippocampal integrity is beneficial for some multi-item retention strategies over DMS delays, but is not critical to this form of maintenance as in the case of configural-relational working memory maintenance. For instance, a common rehearsal strategy is often to replay information during maintenance in the particular order it was presented (Baddeley, 2003). Hippocampal damage is known to affect sequence learning (O'Keefe, 1993) and may impact BHS performance because of an impaired ability to use this particular working memory strategy, yet multi-item

maintenance was not abolished, and therefore not critical, in these tasks compared to configural-relational DMS tasks (Experiment 3A).

On half of the DMS trials a single black and white image of a face was presented (1 sec) during the retention period in order to disrupt working memory maintenance processes. The effect of distraction on working memory performance in the TLE (**Figure 7.2**) and NC (**Figure 7.3**) cohorts are comparable to previous reports (Clapp et al., ; Chao and Knight, 1995; Postle et al., 2005) where task-irrelevant interference has minor effects compared to cognitive 'interruptions' (Experiment 4, - *also see* Clapp et al., 2009) or task-relevant distraction (Chao and Knight, 1998; Postle, 2005; Yoon et al., 2006; Sreenivasan and Jha, 2007).

However, in contrast to current theories of working memory delay interference susceptibility, the presentation of a face distracter during retention periods enhanced DMS performance in the BHS patients (**Figure 7.2** & **Figure 7.3**). The load dependant declines in BHS patient performance (3-item: BHS ($67.8 \pm 12.7\%$) vs. NC ($91.0 \pm 6.01\%$) p=0.0001), and 5-item: (BHS ($70.0 \pm 7.64\%$) vs. NC ($81.0 \pm 7.53\%$) p = 0.012) when compared to the NC (**Figure 7.3**) and similarly when compared to TLE (**Figure 7.2**), were abolished on trials with delay distraction. Therefore, the ability to retain multiple items can be effectively enhanced in patients with BHS by the presentation of brief task-irrelevant information during working memory maintenance. It is important to note, that the BHS patients investigated in this study where considerably older (mean age 43.2; SD 9.8) and were without gainful employment because of their memory difficulties, however, delay distraction improved memory performance to that of young college students (mean age 24.7±3.9). This unexpected and fortuitous enhancement of DMS memory performance in BHS could possibly lead to therapeutic benefits for these patients in the future.

Experiment 7. Task-irrelevant delay distraction during 5-item load DMS with variable maintenance length.

7.6. Aim 7

Next we asked if distraction facilitated memory enhancement is specific to patients where hippocampal integrity is compromised (BHS) or if this is a generalized phenomena that is not related to an anatomical specificity. Although the DMS performance enhancement with distraction was a robust increase compared to without distraction in BHS patients (3-item without distraction, $67.8 \pm 12.7\%$ & with distraction, $81.2 \pm 7.69\%$; 5-item without distraction, $70.0 \pm 7.64\%$ & with distraction, $75.2 \pm 10.9\%$), the patient group displaying this effect was a relatively small group with a very specific neuropathology. We therefore aimed to simulate such delay-dependant deficits in NC participants by extending DMS delay lengths to increase the temporal maintenance demands to the extent in which behavioural performance would match that of the BHS patients (similar delay length manipulation as Experiment 5). In a modified version of the aforementioned DMS task, we asked a group of college aged normal control (NC) participants to maintain 5 black and white pictures of natural scenes (same as 5-item load condition of Experiments 2 & 6) over a variable retention period of 5, 20, or 45 seconds. After which, they were instructed to make the same old/new judgment as Experiment 6 in patients. On 50% of DMS trials, the randomized presentation of a single black and white image of a face for 1 second would appear during the middle of the delay period (**Figure 7.4**).

7.7.1. Participants.

21 healthy subjects (13 female/mean age 23.9 ± 5.5 yrs) participated in this study (one participant was excluded from the study due to not following task instructions). All participants were recruited from the University College of London's Psychology departmental subject pool and were determined to have no extraneous neurological or psychological disorders that would confound our results. In addition, all subjects displayed normal or corrected to normal visual acuity. All participants gave written informed consent to participate and the study was approved by the guidelines of the ethics committee of the University of London Research Ethics Committee for human-based research. All participants were compensated at a rate of £6 per hour for the entirety of the study, which averaged two hours to complete.

7.7.2. Stimuli and Task Design.

The photographic stimuli and visual presentation settings are identical to that of the 5-item load condition of Experiment 6 in patients. This experiment was a 2x3 factorial design consisting of 4 successive DMS blocks with 30 trials per block, resulting in 20 trials per condition. The manipulations in this experiment were delay lengths of 5, 20, or 45 seconds and on half of the trials, a face distracter stimuli (1 sec) was presented during the middle of the delay period. Subjects were instructed to maintain the 5 sample stimuli over a variable delay period whilst fixating on a cross and to ignore the face distracter stimuli. It is important to note that participants were unaware how long they must actively maintain the sample stimuli as there was no prior indication of the delay length of the current trial or if a distracter would be presented during the trial. Targets, foils, delay length, and distracter presentation was randomized and counterbalanced across testing blocks (**Figure 7.4**).
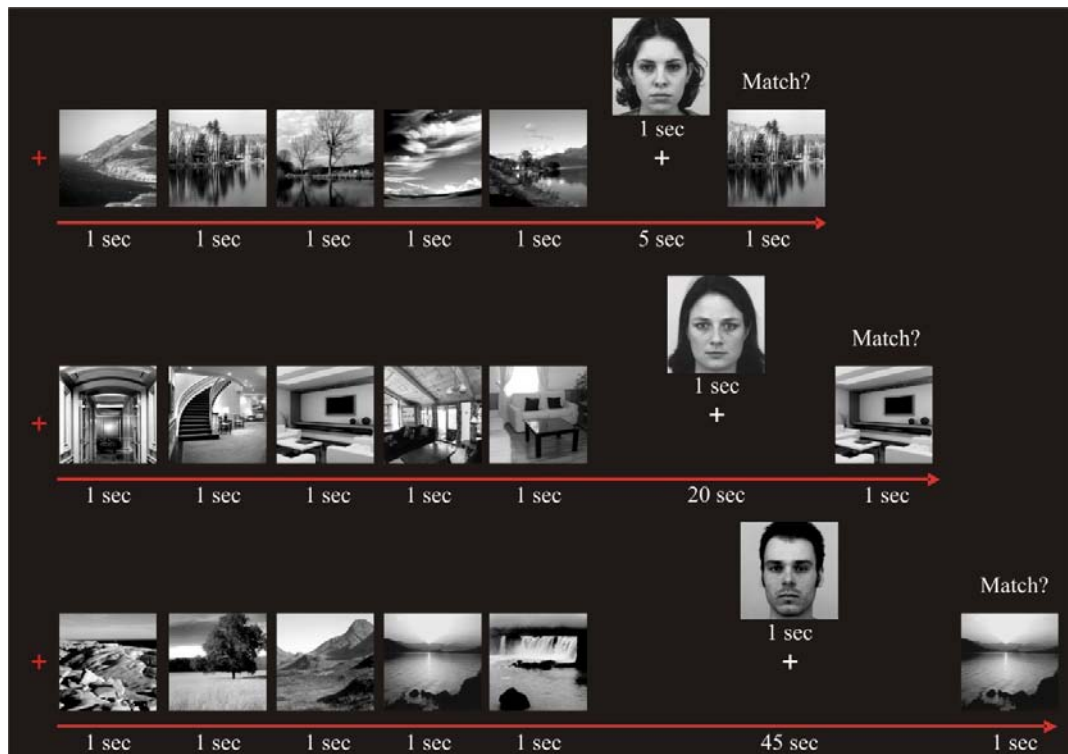
Figure 7.4. 5-item working memory load DMS paradigm. An example of delayed match to sample trials where 5 individual scenes must be maintained over a 5 second (top), 20 second (middle), or 45 second (bottom) delay period in order to make a "match" decision at test. On 50% of trials a face distracter is presented for 1 second.

7.8. Behavioural Results_7_____

7.8.1. DMS task performance.

A 2x3 repeated-measures ANOVA with delay length (5, 20, 45 sec) and distraction (with and without) as the within subjects factor resulted in a main effect for delay length ($F(1.64,31.27) = 6.311$; p=0.008) and trend for distraction ($F(1,19) = 2.171$; p=0.157). Post-hoc paired t-tests (two-tailed, mean, s.e.m.) showed a significant increase in performance when distraction was presented during the 45 second delay (no distraction ($76.25 \pm 2.64\%$) vs. with distraction ($81.25\pm1.74\%$, $t(19)=-2.127$, p = 0.045) – see **Figure 7.5**.

Since memory improvements with distraction were only apparent in the BHS patients when DMS performance fell below 80% (in 3-item and 5-item loading conditions), we performed a median split at this threshold for the 45 sec delay length

condition resulting in two groups: Low performers (< 80%) 9 participants (cumulative percent 45, mean age 25.78 ± 5.09; 5 female) and High performers (≥ 80%) 11 participants (cumulative percent 55, mean age 22.55 ± 5.80; 8 Female). A 2x3 repeated-measures ANOVA (distraction x delay) revealed main effects for delay $(F(1.34, 10.71) = 7.83; p=0.013)$ and distraction $(F(1,8) = 10.0; p=0.013)$, as well as, a strong trend for a delay by distraction interaction $(F(1.79,14.29) = 3.65; p=0.057)$. – see **Table 7.2.**

WML_45

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	.50	1	5.0	5.0	5.0
	.55	1	5.0	5.0	10.0
	.65	2	10.0	10.0	20.0
	.70	3	15.0	15.0	35.0
	.75	2	10.0	10.0	45.0
	.80	6	30.0	30.0	75.0
	.85	2	10.0	10.0	85.0
	.90	1	5.0	5.0	90.0
	.95	2	10.0	10.0	100.0
	Total	20	100.0	100.0	

Table 7.2. Median split at 80% accuracy threshold for the 45 sec delay length condition: Low performers (< 80%) 9 participants (cumulative percent 45) and High performers (≥ 80%) 11 participants (cumulative percent 55).

Post-hoc paired t-tests (two-tailed, mean, s.e.m.) confirmed significantly increased DMS performance in the low performers when a 1 sec distracter is presented during the 45 sec delay period (78.89 ± 3.31%) compared to when no distracter is presented (66.11 ± 2.86%, $t(8)$=-3.944, $p = 0.004$) – see **Figure 7.6**). Additionally, 2x3 repeated-measures ANOVAs and post-hoc paired t-tests in the high performing group do not show any performance enhancement with distraction and in fact, the high performers group seem to do slightly worse with distraction (20 sec delay: no distraction 86.82 ± 3.59%; with distraction 84.55 ± 3.66%, $t(10)$= 0.959, $p = 0.360$; & 45 sec delay: no distraction 84.55 ± 1.84%; with distraction 83.18 ± 1.55%, $t(10)$= 0.760, $p = 0.465$) – see **Figure 7.7**.

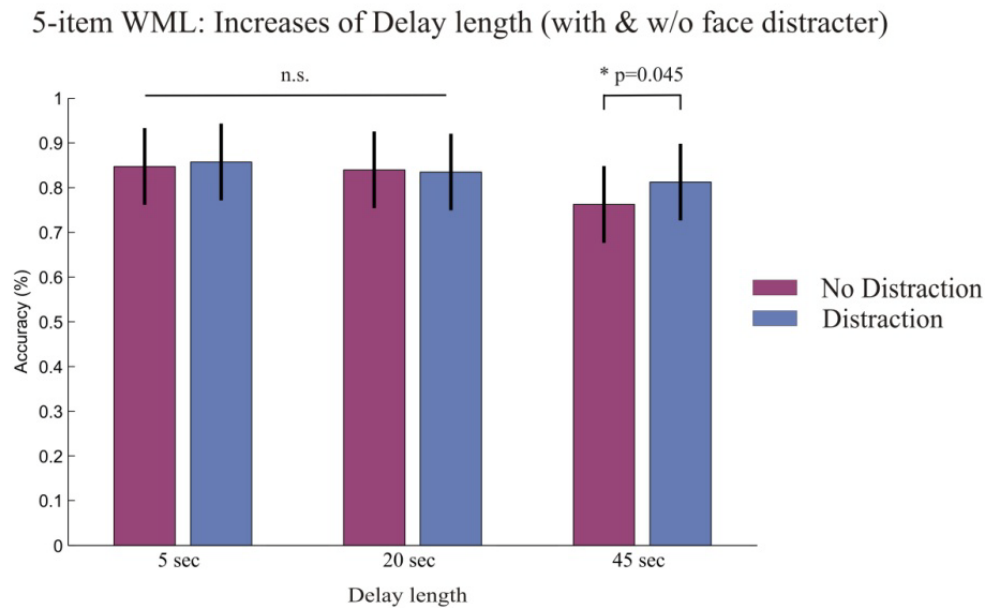5-item WML: Increases of Delay length (with & w/o face distracter)

Figure 7.5. Mean DMS accuracy for normal controls (NC) when required to maintain 5 scenes over a 5 second, 20 second, or 45 delay period (no distraction in purple). On half of the trials, a 1 second face distracter would appear (blue) during the middle of the delay. When DMS performance was sufficiently decreased by the temporal demands of extended maintenance (i.e. 45 seconds) task-irrelevant delay distraction significantly increased DMS performance.

7.9. Interim Discussion 7

Extending the 5-item retention interval to 45 seconds in the NC group (main effect for delay length (F $(1.64, 31.27) = 6.311$; p=0.008) sufficiently modelled BHS multi-item performance deficits at shorter delay lengths (NC 5-item: $76.25 \pm 2.64\%$; BHS 5-item: $70.0 \pm 7.64\%$). Analogous to the memory enhancement found in BHS patients, on DMS trials in which a face stimulus was presented during this extended delay period resulted in a significant increase in memory performance in NC ($81.25 \pm 1.74\%$, $t(19)=-2.127$, p $= 0.045$) – see **Figure 7.5.**

Since increases in BHS patients' memory performance were profoundly more robust after performance fell below a critical threshold ($< 80\%$ in 3 and 5-item load) and similarly in NC ($< 80\%$ in 45 sec delay length), we performed a median split at this threshold creating a 'low performance' NC group to more accurately model the load-dependant deficits of the BHS patients (**Table 7.2**). When the accuracy of the low performance group fell below this threshold (45 sec delay: $66.11 \pm 2.86\%$) and

matched that of BHS patients (3-item: 67.8 ± 12.7% and 5-item: 70.0 ± 7.64%), the presence of distracter stimuli during the retention interval significantly improved memory performance (78.89 ± 3.31%, t (8) =-3.944, p = 0.004) – see **Figure7.6**. Task-irrelevant distraction raised memory performance to the same level as the minimal delay length condition (5 sec delay: 81.67 ± 4.33%), thereby effectively abolishing any delay length related memory deficit at 45 seconds.
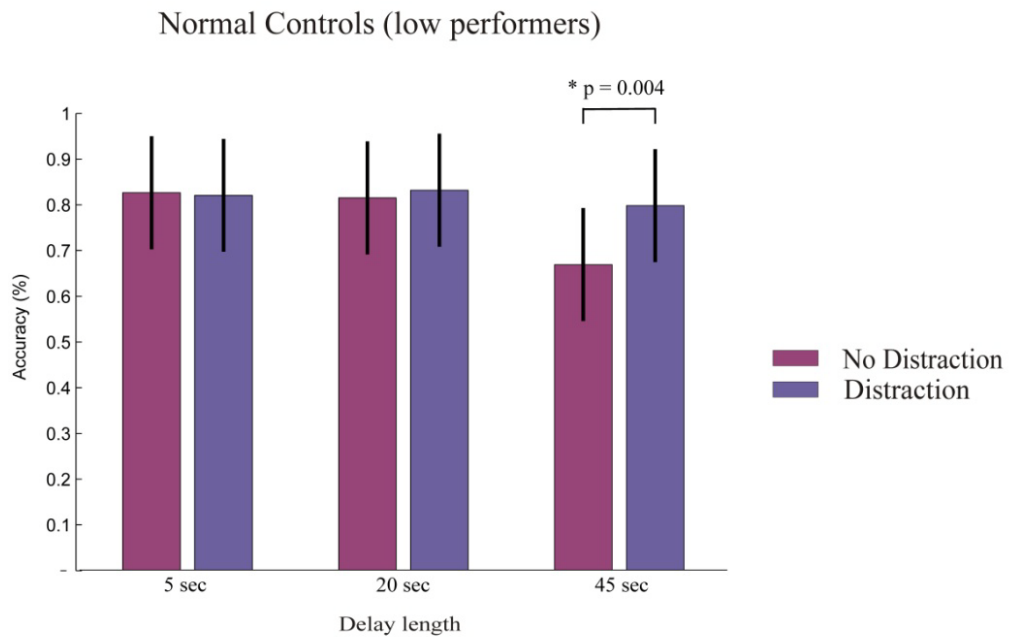

Figure 7.6. Mean DMS accuracy for Low Performers when required to maintain 5 individual scenes over a 5 second, 20 second, or 45 delay period (no distraction in purple & with distraction in blue). When accuracy of the low performance group without distraction (45 sec delay: 66.11 ± 2.86%) matched that of BHS patients (3-item: 67.8 ± 12.7% and 5-item: 70.0 ± 7.64%), the presence of task-irrelevant distracter stimuli during the retention interval significantly improved memory performance.

In the high performance NC group no such memory improvement was found with delay distraction (**Figure 7.7**). Additionally, high and low group comparisons showed a strong trend for a delay by distraction interaction (F (1.79, 14.29) = 3.65; p=0.057) suggesting that distraction facilitated memory enhancement must be contingent on differential maintenance processes that underlie the behavioural correlates found between these groups.

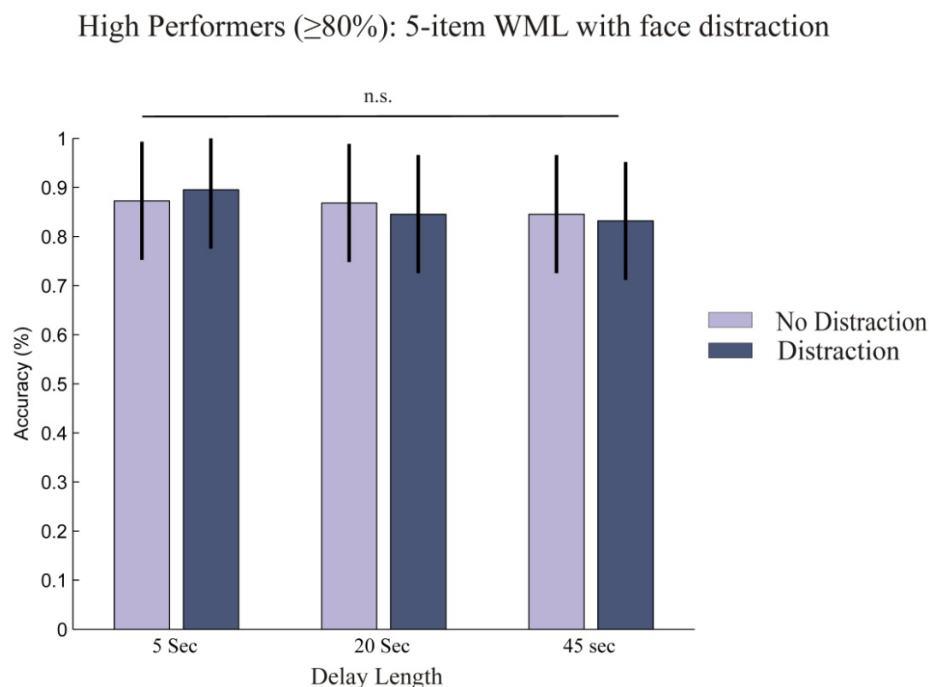High Performers (≥80%): 5-item WML with face distraction

Figure 7.7. Mean DMS accuracy for High Performers when required to maintain 5 individual scenes over a 5 second, 20 second, or 45 delay period (no distraction in purple & with distraction in blue). In the high performance NC group no such memory improvement was found with delay distraction

Experiment 8. High-load theta maintenance disruption by task-irrelevant distraction

7.10. Aim 8

Are task-irrelevant stimuli during working memory delays actually distracting? One question that arises from Experiment 6 and 7, is if face stimuli presented during the retention interval are facilitating maintenance processes (working memory enhancement) or disrupting online retention (working memory disruption) and thereby allowing a more accurate alternative memory trace to persist more clearly.

Bilateral regions of the pre-frontal cortex have been shown to be directly affected by the quantitative loading of individual items in working memory (Postle, 2006; Zhu et al., 2006; Dolcos et al., 2007). In Experiment 3, we demonstrated that

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load-dependant increases of bi-frontal theta phase-coupling reflected high-load maintenance of multiple items during the DMS retention interval maintenance using the same study design as used here in Experiment 6. Therefore, to test if distracter stimuli during multi-item retention enhances or disrupts maintenance processes, we analysed the bi-frontal theta phase-coupling from the NC participants of Experiment 2 that underwent MEG recordings during testing (*see* Chapter 3 methods). We previously demonstrated load-dependant increases of theta synchronization between frontal sensors to be significantly enhanced during the early portion of delay periods, but eventually diminished as the retention interval persisted (**Figure 3.5B**).

7.11. Magnetoencephalography Results 8

7.11.1. Phase Coupling Analysis.

To test our hypothesis that the presentation of task-irrelevant stimuli during delay periods of the DMS task will disrupt high-load theta-coupling maintenance, we re-analyzed 6 Hz phase-coupling during the retention interval of the high-load condition (5-item) in the same 10 healthy participants of Experiment 2. The MEG participants' data was split into two groups based on the median performance of the high load condition without distraction (same as Experiment 7): Low performers ($\leq$ 80%) 5 participants (cumulative percent 50, mean age 26.8 $\pm$ 7.5; 4 female) and High performers (> 80%) 5 participants (cumulative percent 50, mean age 22.8 $\pm$ 2.8; 4 Female).

The low performers group displayed the same trend of increased 5-item DMS performance with task-irrelevant distraction (74.6 $\pm$ 1.75% vs. 79.4 $\pm$ 3.78%) as BHS patients (Experiment 6) and as the low performers group in normal controls (Experiment 7), but this improvement did not reach significance due to a small sample size ($p > 0.05$). However, independent samples t-tests between groups do confirm significant differences between high and low performers without distraction (86.6 $\pm$ 1.36% vs. 74.6 $\pm$ 1.75% *respectively*; $t(8) = 5.41$, $p = 0.001$), while these group differences are abolished with delay distraction ($p > 0.05$). **– Figure 7.8.**
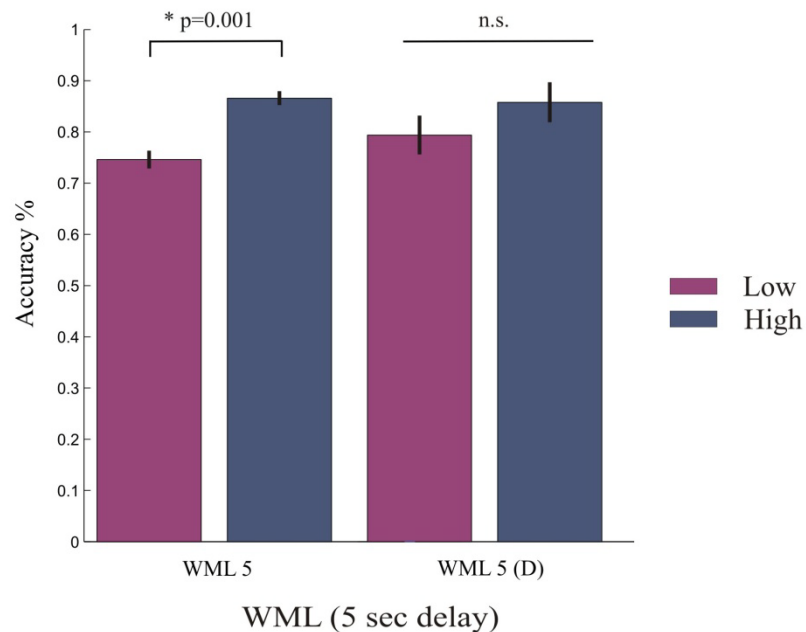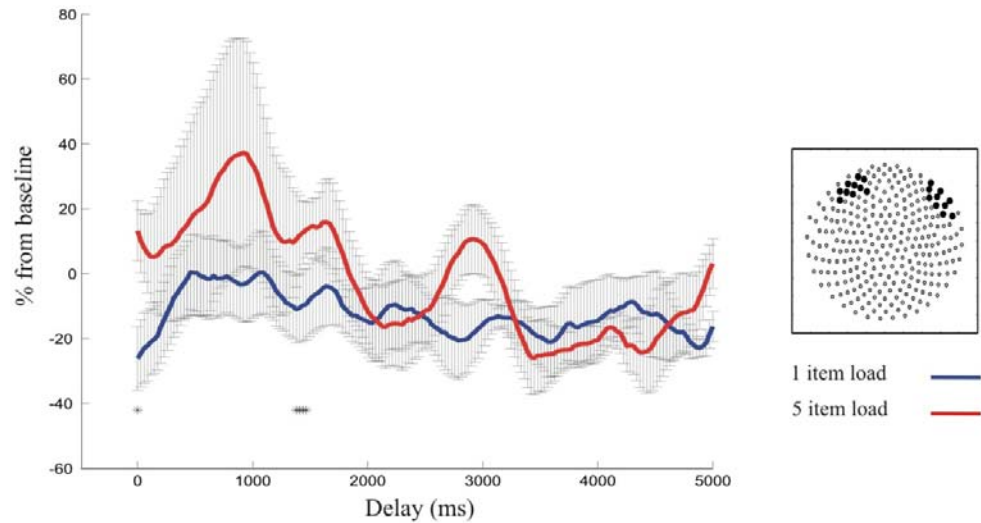
5 item load: Low vs. High Performers

Figure 7.8. The MEG participants' data was split into two groups based on the median performance of the high load condition without distraction (same as Experiment 8): Low performers (≤ 80%) 5 participants (cumulative percent 50) and High performers (> 80%) 5 participants (cumulative percent 50).

Within group serial measures t-tests (p<0.05 threshold) on bi-frontal sensor groups of the low performer group revealed significantly increased theta-coupling for 5-item load vs. 1-item load (**Figure 7.9B**). This elevated bi-frontal coupling was evident soon after stimulus offset and steadily rises across the delay period. In contrast, high performers had a similar trend for increased bi-frontal coupling soon after stimulus offset (5 vs. 1-item load); however this enhancement dissipates over the course of the delay (**Figure 7.9A**). Between group t-test comparisons of the 5-item load condition (independent samples t-test, same threshold as above) on similar sensor groups significantly contrast the bi-frontal theta-coupling decrement in the high performer group while the low performers coupling steady increases over the course of the delay (**Figure 7.10**).

Figure 7.9. Serial measures t-test comparisons of 6 Hz phase-coupling on selected sensor groups (shown on right-side insets) for non-configural-relational low working memory load ('1 item load' in blue) vs. high working memory load ('5 item load' in red) delayed-match-to-sample (DMS) conditions in Experiment 8 (threshold of p<0.05 per time point if present continuously over three successive theta cycles indicated by markings on *x*-axis). In high performers (A), bi-frontal theta coupling is enhanced in the early portion of the delay period for 5-item load vs. 1-item load, and this coupling dissipates over the course of the delay similar to Experiment 2. However, in low performers (B) this bi-frontal theta coupling enhancement for 5-item load maintenance continues throughout the delay.

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Within group serial measures t-tests (p<0.05 threshold) contrasting 5-item load with and without delay distraction in the low performers group shows significant disruption of bi-frontal coupling after distracter presentation (~2000 ms) compared to the increased coupling of the no distracter condition (**Figure 7.11A**). This disruption of theta-coupling after distraction continues throughout the rest of the delay, a pattern that mimics the same temporal pattern of activity of the high performing group when no distraction is presented (**Figure 7.12**). In contrast, the 5-item load condition (with and without distraction) of the high performing group resulted in no significant theta-coupling differences of bi-frontal sensor groups (**Figure 7.11B**), as well as no behavioural impact of distraction (**Figure 7.8**).

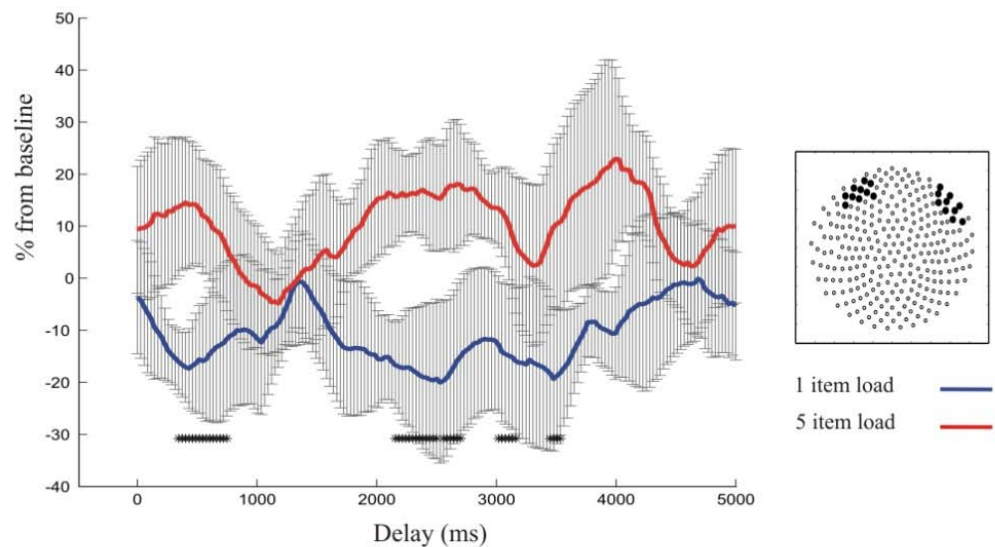**Figure 7.10. Serial measures t-test comparisons of 6 Hz phase-coupling on selected sensor groups (shown on right-side insets) for the '5 item load' delayed-match-to-sample (DMS) conditions comparing low performers (blue) vs. high performers (red) in Experiment 9 (threshold of p<0.05 per time point if present continuously over three successive theta cycles indicated by markings on *x*-axis). Bi-frontal theta-coupling of the high performance group clearly declines over the course of the delay period, while low performers bi-frontal engagement persists across the entire delay.**

A Low performers: 5 item load with/out distraction

No Distraction —
Distraction —

Distraction (1000 ms)
500 ms jitter

B High performers: 5 item load with/out distraction

No Distraction —
Distraction —

Distraction (1000 ms)
500 ms jitter

Figure 7.11. Serial measures t-test comparisons of 6 Hz phase-coupling on selected sensor groups (shown on right-side insets) for 5-item working memory load with no distraction (blue) vs. with distraction (red) delayed-match-to-sample (DMS) conditions in Experiment 9 (threshold of $p<0.05$ per time point if present continuously over three successive theta cycles indicated by markings on *x*-axis). In low performers (A), bi-frontal theta coupling enhancement is

disrupted with face distraction, while this coupling increases throughout the delay without delay distraction. In contrast, high performers (B) show no differences between bi-frontal theta-coupling with or without delay distraction.

7.12. Interim discussion 8

In Experiment 2, we demonstrated load-dependant increases of theta synchronization between frontal sensors to be significantly enhanced during the early portion of delay periods, but eventually diminished as the retention interval persisted (**Figure 3.5B**). However, when these participants are separated into high and low performance groups (based on 5-item load accuracy), the high performers display a similar pattern of initial bilateral frontal theta phase-coupling enhancement for 5-item (vs. 1-item) maintenance that subsides over time (**Figure 7.9A**). Alternatively, the low performance group also display this initial pattern, however bi-frontal theta engagement significantly increases over the course of the entire delay period (**Figure 7.9B**). Direct comparisons of high and low performance groups confirm significant theta-synchrony decreases in the later portion of the delay for participants with more accurate 5-item memory performance (**Figure 7.10**). Therefore, the online retention of multiple items seems to become adversely affected by the continued persistence of bilateral coupling across delay periods, as in the case of low performing NC participants (**Figure 7.8**).

We hypothesized that if continued theta-coupling of frontal sensors across the later portion of the delay period reflects a faulty or 'noisy' maintenance representation (as in the case of the low performance group), then distracter stimuli presented during the retention period would effectively disrupt this bi-frontal coupling. As expected, task-irrelevant distraction (presented ~2000ms) completely disrupts bi-frontal theta high-load maintenance processes in the low performance group when compared to 5-item load delay activity without distraction (**Figure 7.11A**). Furthermore, the temporal pattern of theta synchronous activity in these regions after distraction in the low performers are almost identical to that of the high performance group when no distraction is present (**Figure 7.12**). This convergence of behavioural and functional evidence strongly suggests that the persistence of faulty high-load maintenance can be disrupted by task-irrelevant distraction and thereby mimicking endogenous neural mechanisms that facilitate better performance,

as in the case of the high performance group. Consistent with this notion, the presence of distracter stimuli during delay maintenance in the high performance group showed no significant effect on bi-frontal theta coupling (**Figure 7.11B**) or on performance (**Figure 7.8**).
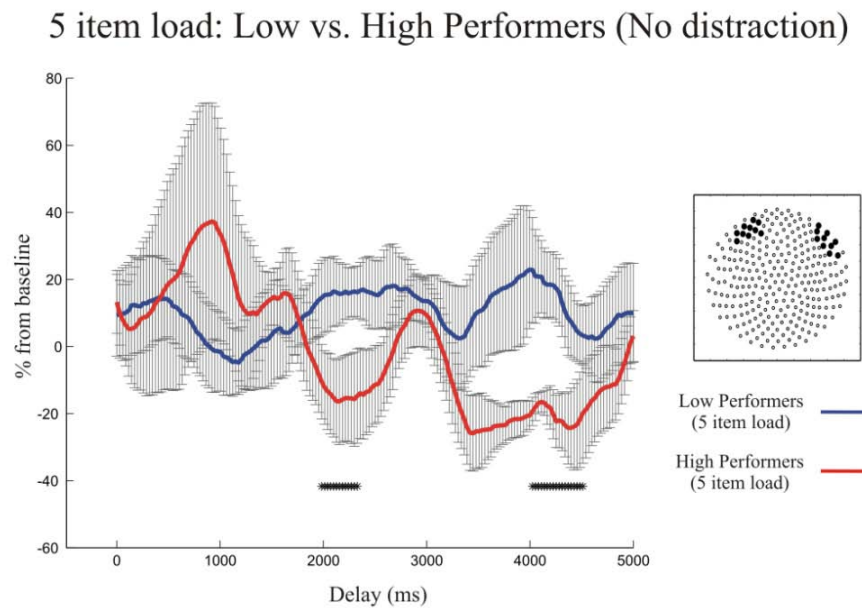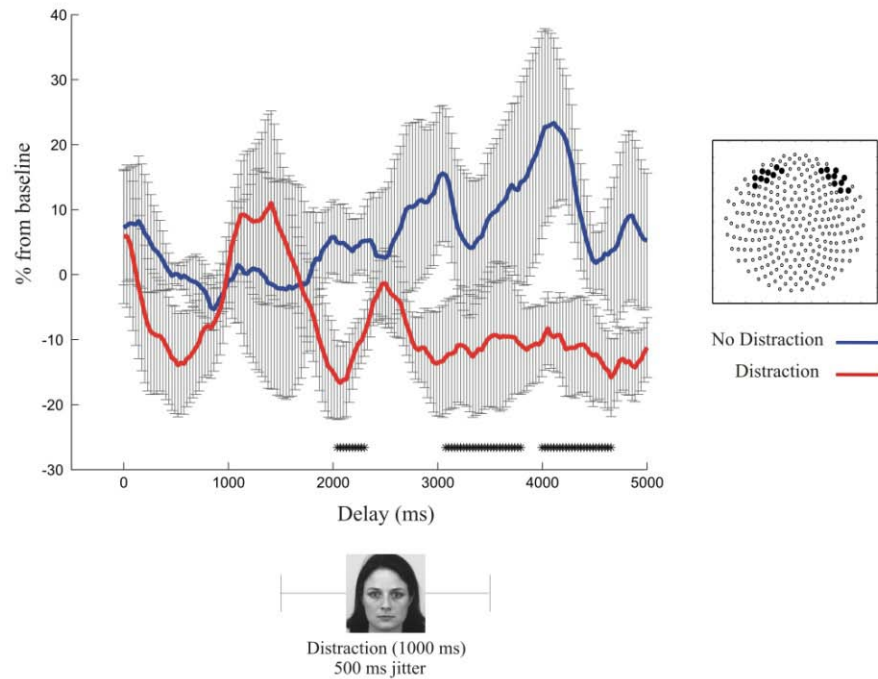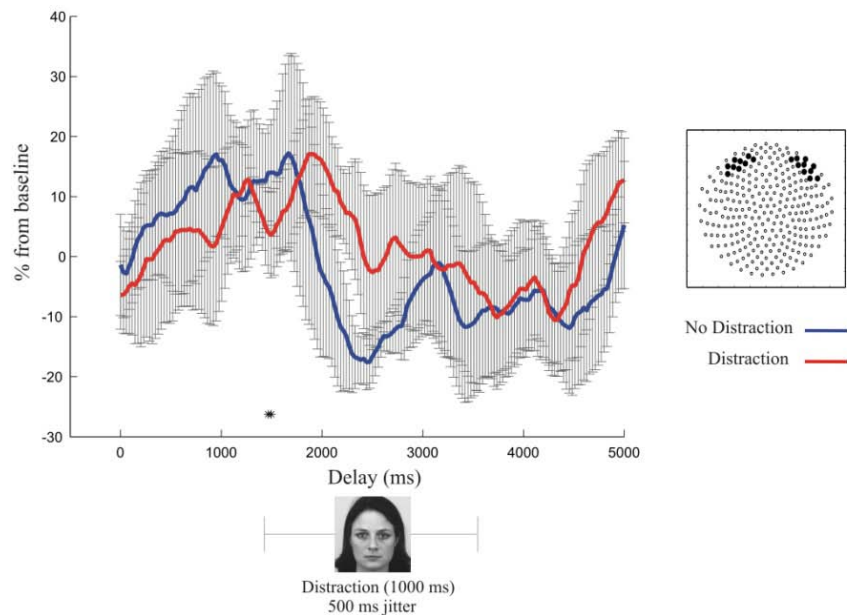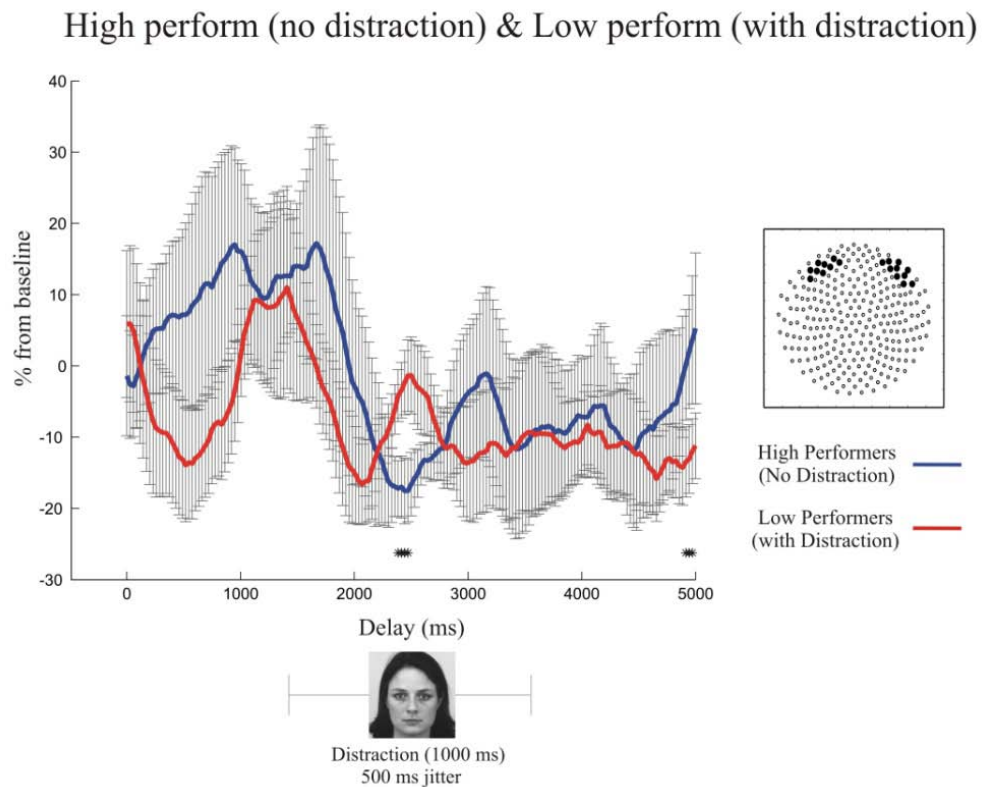

Figure 7.12. Serial measures t-test comparisons of 6 Hz phase-coupling on selected sensor groups (shown on right-side insets) for 5-item working memory load in the high performance group with no distraction (blue) vs. the low performance group with distraction (red) delayed-match-to-sample (DMS) conditions in Experiment 8 (threshold of p<0.05 per time point if present continuously over three successive theta cycles indicated by markings on *x*-axis). The temporal pattern of theta synchronous activity in these regions after distraction in the low performers are almost identical to that of the high performance group when no distraction is present.

7.13. Final Discussion

In this chapter we show that task-irrelevant distraction can improve high-load DMS performance in BHS patients (Experiment 6) and in similar conditions where healthy participants maintain a 'faulty' working memory representation, as in the case of extended delay period lengths (Experiment 7). Furthermore, we demonstrate that in such cases, task-irrelevant distraction is disrupting prefrontal theta-network maintenance (Experiment 8). These results call into question what form of memory performance is being enhanced by task-irrelevant distraction.

The short-term retention of certain forms of visual information in working memory have been shown to be intimately linked to long-term memory processes (Ranganath et al., 2005) and specifically to regions of the medial temporal lobe dedicated to long-term memory (Experiment 3A, *also see* - (Hannula et al., 2006; Hannula and Ranganath, 2008). Furthermore, successful long-term memory encoding and subsequent delayed recognition memory retrieval have been shown to be greatly facilitated by working memory maintenance of the same items (Experiment 3C, *also see* – (Schon et al., 2004; Ranganath et al., 2005; Khader et al., 2007) suggesting a common limited resource allocation for both stimulus maintenance and encoding As a direct consequence, when multiple representations held in working memory are incomplete or faulty, then continued maintenance of these items will interfere with later long-term memory recognition (Axmacher et al., 2009; 2010).

Consistent with these results, when faulty working memory maintenance persists (high load conditions in BHS –Experiment 6) or becomes faulty due to delay lengths exceeding the ability of working memory resources (45 sec delay in low performers – Experiment 7), there was a related decrease in performance when maintenance relies purely on frontal theta working memory mechanisms. Alternatively, if faulty maintenance is disrupted in such cases by task-irrelevant distraction (Experiment 8), then a more accurate alternate memory signal is allowed persist, thereby increasing DMS performance.

Radiological reports confirm medial temporal lobe damage in these BHS patients is confined to the hippocampi bilaterally (see Chapter 4), thus it is unlikely that any hippocampus-dependant memory processes can account for distracter facilitated memory enhancement. However, since regions of the rhinal cortex are

thought to be spared in these patients, one possible explanation is that disrupting faulty maintenance (via interruption of bi-frontal theta-coupling) allows familiarity-based judgements to become unclouded by a noisy working memory representation. Evidence that familiarity-based recognition is dependent on the perirhinal cortex and not on hippocampal integrity supports such a notion - *for review see* (Eichenbaum et al., 2007).

Alternatively, it could be hypothesized that the presentation of task-irrelevant stimuli during delays enhances vigilance or attention to current task goals (i.e. working memory enhancement) by cueing participants to stay on task. However, such an account seems contrary to previous evidence showing regions of the pre-frontal cortex specifically tuned to cope with increases in working memory demands (Fuster and Alexander, 1971; Goldman-Rakic, 1996; Jensen and Tesche, 2002; Onton et al., 2005; Deiber et al., 2007; Artchakov et al., 2009) and resistance to distraction (Chao and Knight, 1998; Miller and Cohen, 2001; Artchakov et al., 2009). Similarly, we demonstrated that engagement of theta-coupling between bi-frontal regions are enhanced with increases of working memory demands in NC (Experiment 2), however, the temporal attenuation of this activity over the course of retention, either endogenously (high performers- **Figure 7.9A**) or by exogenous distraction (low performers- **Figure 7.9B**), suggests an optimal window of prefrontal engagement that supports delay performance. Recent electrophysiological evidence highlighting the differential effects of variable distracter presentation during working memory delays (Artchakov et al., 2009) support this possibility. Although it seems unlikely that late delay decreases in pre-frontal engagement would reflect an increase in participants' vigilance to current task demands, further investigation is necessary to determine the exact nature of cortical processing responsible for the improvement in memory performance reported in this chapter.

It has been well established that the maintenance of visual representations become more susceptible to interference from distraction when the capacity of working memory is quantitatively 'loaded' by increases of information (Chao and Knight, 1995; Baddeley, 1998; Chao and Knight, 1998; Baddeley, 2003). However, in contrast to current theories, we found that task-irrelevant distraction during delay periods improved DMS performance in BHS patients. This memory enhancement was robust enough to raise the BHS patients' performance to the same level of college age healthy controls. Additionally, we show that in similar conditions where

healthy participants maintain a 'faulty' working memory representation, as in the case of extended delay period lengths, task-irrelevant distraction can increase performance in participants to such an extent that any delay period impairment is abolished.

The bilateral synchronization of frontal brain regions within the theta frequency band are characteristic of maintaining increases of visual information in working memory. Using MEG we establish that, paradoxically, the persistence of visual information is impeded when this bi-frontal theta maintenance process exceeds a time dependant optimal efficiency. In such cases, disrupting this coupling mechanism with task-irrelevant distraction allows for a more accurate long-term memory signal to persist, thereby improving performance. Our findings elucidate an important functional interaction between short-term working memory and long-term memory processes and have potential therapeutic implications for patients suffering from memory impairments.

7.14. Summary

In contrast to current theories, we found that task-irrelevant distraction during delay periods improved DMS performance in patients with bilateral hippocampal sclerosis (BHS). This memory enhancement was robust enough to raise the BHS patients' performance to the same level of college age healthy controls. Additionally, we show that in similar conditions where healthy participants maintain a 'faulty' working memory representation, as in the case of extended delay period lengths, task-irrelevant distraction can increase performance in participants to such an extent that any delay period impairment is abolished. The bilateral synchronization of frontal brain regions within the theta frequency band are a characteristic of maintaining increased working memory load. Here we demonstrate that the persistence of visual information is impeded when this bi-frontal theta maintenance process exceeds a time dependant optimal efficiency. In such cases, disrupting this coupling mechanism with task-irrelevant distraction allows for a more accurate long-term memory signal to persist, thereby improving performance.

VIII. Conclusion

In a series of working memory experiments using Magnetoencephalography (MEG) we investigated cortical synchronization within the theta band during the active maintenance of configural-relational or non-configural-relational visual stimuli in delayed-match-to-sample tasks (DMS) in healthy adults and patients with bilateral hippocampal lesions. Using this approach we provide converging evidence for a critical role of hippocampus-dependent cortical theta-synchrony in the active maintenance of configural-relational visual information. We also demonstrate that this theta-synchrony, coupling occipito-temporal and fronto-temporal sensors, is functionally and anatomically dissociated from non-configural-relational visual maintenance, which engaged theta synchrony between frontal and parietal sensors. Furthermore, increasing the working memory load in the absence of configural-relational maintenance demands engaged bilateral frontal theta-synchrony. This indicates that occipito-temporal theta synchrony in configural-relational maintenance cannot be accounted for by the additional demands of maintaining more scene elements. Although patients with bilateral hippocampal damage do display decreased performance in multi-item working memory maintenance, this deficit can be effectively abolished by the presentation of task-irrelevant distraction during delay periods. Similarly in healthy participants, when faulty working memory maintenance mechanisms (i.e. bi-frontal theta-coupling) are disrupted by task-irrelevant distraction, memory performance may be enhanced by allowing a more accurate hippocampal-independent alternative memory trace to persist. We provide functional, behavioural, and anatomical evidence for complex interactions between long-term and short-term memory challenging the classical distinction between these forms of memory where functional and anatomical commonalities may be shared by both.

8.1. Closing Discussion

The persistence of stimuli in working memory is not a temporally locked phenomenon, but one that evolves over time, and therefore we chose investigate the neural dynamics of delay maintenance by induced oscillatory activity. Furthermore, we chose to investigate oscillatory activity specifically within the theta band because of its intrinsic properties of integrating the functional cooperation of distant assemblies into a coherent network (Jones and Wilson, 2005; Sarnthein et al., 1998). We utilized this framework to investigate how the brain's rhythmic oscillations of neural activity can synchronize to create functional networks of stimulus persistence in working memory. In Experiment 1 we demonstrate cortical synchronization during the active maintenance of the configural relationships of visual information was characterized by the induced theta-synchronous coupling of fronto-temporal and occipito-temporal brain regions. While non-configural-relational forms of maintenance using identical stimuli engaged a theta-coupled network involving frontal and parietal areas more commonly reported in working memory maintenance (Cohen et al., 1997; Courtney et al., 1997; Baddeley, 1998; Sarnthein et al., 1998; D'Esposito et al., 2000; Haxby et al., 2000; Postle et al., 2000; von Stein and Sarnthein, 2000; Deiber et al., 2007).

Recently it has been demonstrated that amnesic patients with selective hippocampal atrophy, not only have profound long-term memory impairments (Lavenex and Amaral, 2000; Squire and Zola-Morgan, 1991), but also display working memory deficits for the spatial configuration of objects over short delay periods (Hannula et al., 2006; Olson et al., 2006a). Consistent with this notion, we show that patients with bilateral hippocampal sclerosis (BHS) could not remember images after 60 minutes of exposure, but performed normally when the retention interval was only 5 seconds for non-configural-relational working memory tasks (Experiment 3C). These patients also displayed preserved fronto-parietal theta synchronization during working memory retention intervals (Experiment 3B).

Importantly, BHS patients' ability to retain the configural relationships within scenes over brief intervals was severely impaired and this was accompanied by a selective abolishment of occipito-temporal theta synchrony (Experiment 3A & 3B). These results are consistent with the functional coordination of cortical activity by hippocampal driven theta previously reported in rodents (Sirota et al., 2008; Jones

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and Wilson, 2005; Siapas et al., 2005) and was the first to demonstrate that the hippocampus is functionally critical to this network in human working memory. Furthermore, fronto-parietal theta engagement was evident in both configural-relational and non-configural-relational delay periods in BHS, suggesting that when hippocampal integrity is compromised, the "classic" working memory network is engaged, but cannot functionally support the additional maintenance requirements of configural-relational representations (Experiment 3B).

Together, these results emphasize the critical role of hippocampal theta synchronization to coordinate occipital and temporal brain regions during short-term working memory delays of configural-relational information. This theta network may contribute to the associative integration of visual elements in the rostral portions of the ventral visual stream, such as the rhinal cortex, with the individual component features in more posterior regions (e.g., visual areas such as V4) (Bussey and Saksida, 2002; Ryan and Cohen, 2004; Aggleton et al., 2007; Hannula and Ranganath, 2008) and thereby allowing a holistic representation to persist. Possibly through feedback connections to the cortex, hippocampal neurons can activate a more detailed, lower-level representation that is stored in the cortex which would be needed for the retention of specific configural features in complex visual stimuli (Lisman and Idiart, 1995; Olson et al., 2006b; Hannula and Ranganath, 2008). This could be accomplished by the periodic reactivation of single visual features (Fuentamilla et al., 2010) from the ventral visual stream, thus favouring auto-associative binding of several parts into a meaningful whole.

In contrast, non-spatial information maintenance would be linked to the reactivation of mental representations in the absence of vivid sensory details stored in the visual stream (Haxby et al., 2000), thus engaging the participation of frontal and posterior associative cortical regions previously reported in object-based working memory maintenance (Fuster and Alexander, 1971; Sarnthein et al., 1998), yet still functionally interconnected through the organisational properties of theta synchrony (Sarnthein et al., 1998). Through theta oscillations the hippocampus may drive the reciprocal exchange of information with neocortical areas during configural-relational maintenance (Sirota et al., 2008). According to this suggestion, the hippocampus may actively control the transfer of neocortical information to the hippocampus itself via theta-phase biasing of neocortical network dynamics (Sirota et al., 2008). This hippocampally dependent mechanism of relational binding of

visual information from neocortical regions may be ubiquitous to the retention of contextual associations for both long-term and short-term memory.

Previous behavioural studies in patients with hippocampal sclerosis have also found deficits in binding the features of a scene being already present at encoding (Hannula and Ranganath, 2008), suggesting possible underlying perceptual deficits in these patients when performing visual discrimination. In a recent fMRI study, short-term memory for object-location relationships was determined during the encoding related activation of the hippocampus (Hannula and Ranganath, 2008). Occipito-temporal synchrony of configural-relational working memory was found to be initially engaged during encoding and then extended into the delay period for individuals without hippocampal damage, while in BHS patients theta synchrony was abolished already during stimulus encoding (Experiment 3B). Similar deficits in the early encoding of declarative long-term memory processes have recently been reported in patients with hippocampal lesions (Dewer et al., 2007). It has therefore been hypothesized that the underlying causes of the characteristic amnesic impairments in patients such as "H.M.", might be due to a deficit in the consolidation of new information and not in the retrieval of this information, as initially proposed (Scoville and Milner, 1957; Lavenex and Amaral, 2000; Squire and Zola-Morgan, 1991). These findings suggest that bilateral hippocampal injury may impair cooperative binding of information distributed across occipital and temporal regions initially during encoding and the deficits observed during delay periods may be an extension of this problem.

In Experiment 2, we demonstrated that increasing the number of scene images that had to be retained during the delay from one to five was associated with increased theta coupling of bilateral frontal and temporal sensors. This pattern is very similar to increases in frontal theta-coupling during working memory loading tasks found previously in EEG studies (Deiber et al., 2007). Most importantly, the bi-frontal theta synchrony due to increased working memory load was non-overlapping with the occipito-temporal theta-synchrony of configural-relational maintenance, indicating that dissociable networks are responsible for supporting the separate maintenance demands of item loading and configural-relational representations. This strongly argues against the possibility that functional differences between the configural-relational and non-configural-relational

maintenance conditions are due to increases in working memory load in the configural-relational condition.

When BHS patients were required to actively maintain more than one image in their mind, DMS performance did decreased when compared to the temporal lobe epilepsy control group with no hippocampal reductions (TLE) and college age normal controls (NC). This suggests that the hippocampus may contribute to some compensatory mechanisms of multi-item working memory maintenance. However, it is important to note the decreases in 3 and 5 –item load DMS performance in BHS (Experiment 6) were not nearly as profound as the configural-relational DMS impairments for BHS patients compared to temporal lobe epilepsy patients without hippocampal damage in Experiment 3A. It is therefore likely that the hippocampal integrity is beneficial for some multi-item retention strategies (i.e. sequence rehearsal), but is not critical to this form of maintenance as in the case of configural-relational working memory maintenance because multi-item maintenance was not completely abolished. These results are compatible with recent studies showing that patients with medial temporal lobe amnesia showed a selective impairment in the ability to maintain relational conjunctions in working memory but had no memory load related impairment (Olson et al., 2006; Finke et al., 2008).

Delayed recognition memory for scenes from the configural-relational DMS trials in normal controls and LTN patients (Experiment 3C) were significantly better than for scenes from the non-configural-relational DMS trials. Importantly, delayed recognition memory for both types of samples was at chance in patients with BHS (Experiment 3C), despite the fact that these patients were unimpaired in the working memory performance for non-configural-relational stimuli (Experiment 3A), as well as, displayed intact fronto-parietal synchrony (Experiment 3B). These findings suggest that the hippocampus-dependent theta coordination of occipito-temporal and fronto-temporal regions during configural-relational maintenance also contributed to encoding into long-term memory but this was not the case for the hippocampus-independent fronto-parietal theta synchrony. These results are compatible with the suggestion that hippocampal maintenance operations may contribute to long term memory encoding (Hannula and Ranganath, 2008; Ryan and Cohen, 2004; Ezzyat and Olson, 2008). Likewise, configural-relational DMS performance remained relatively constant for up to 30 seconds of maintenance, while high-load non-configural-relational maintenance performance declined within this time frame

(Experiment 4). Together these results support the possibility of a link between hippocampus-dependent theta network contributions to working memory maintenance and encoding into long-term memory.

However, it is still argued that hippocampus is not critical for working memory maintenance and that contributions of medial temporal lobe are only in cases where working memory capacity is exceeded and long-term memory processes compensate for additional maintenance demands (Shrager et al., 2008). Furthermore, it has been proposed then that the key hallmark of working memory is its susceptibility to interference during delay periods (Shrager et al., 2008), in which long-term memory is resilient. Under this assumption, a recent behavioural study has shown that hippocampal damaged patients only display short-term memory deficits under conditions where individuals with normal hippocampi are not susceptible to delay interference (i.e. stimulus retention relies on long-term memory - Shrager et al., 2008).

To address this hypothesis directly, we demonstrated that task-relevant interference presented during delays disrupts configural-relational working memory maintenance to the same degree as high item load working memory (Experiment 5). Also, theta synchronization of bi-frontal cortical regions for high working memory load (Experiment 2) was completely non-overlapping with the occipito-temporal synchrony of configural-relational working memory maintenance (Experiment 1). These results strongly support configural-relational maintenance as a hippocampally dependant process akin to working memory maintenance where behavioural, functional, and anatomical commonalities are shared by both short- and long-term memory.

It has been demonstrated that successful long-term memory encoding and subsequent delayed recognition memory retrieval have been shown to be greatly facilitated by working memory maintenance of the same items (Schon et al, 2004; Ranganath et al, 2005; Khader et al., 2007) highlighting a functional interaction of both short-term stimulus maintenance and long-term memory encoding. As a direct consequence of such an interaction, when multiple representations held in working memory are incomplete or faulty, then continued maintenance of these items will interfere with later long-term memory recognition (Axmacher et al., 2009, 2010). One serendipitous result of such an interaction between long-term and short-term memory is the finding that task-irrelevant distraction during delay periods improved

DMS task performance in patients with bilateral hippocampal sclerosis (BHS). Furthermore, that this memory enhancement was robust enough to raise the BHS patients' performance to the same level of college age healthy controls (Experiment 6). Not only does this support the notion that what is rehearsed or maintained in working memory can update and interact with representations in long-term memory (Baddeley, 2003), but also has important implications for individuals suffering from these forms of memory impairments.

Additionally, by extending delay lengths of DMS retention interval we were able to behaviourally match high-load performance of normal controls to that of BHS patients. Under such conditions, a continued interaction of representations in working memory seem to interfere with rapidly formed long-term memory representations. Furthermore, disrupting working memory rehearsal by task-irrelevant distraction can thereby effectively improve memory performance in such conditions. We demonstrate this possibility in the case of extended DMS delay period lengths in normal controls where task-irrelevant distraction increased performance to such an extent that any delay period impairment was abolished (Experiment 7).

Furthermore, we highlight a neural correlate of this phenomena where the persistence of high load working memory can be impeded when bi-frontal theta maintenance processes exceeds a time dependant optimal efficiency. In Experiment 3, we show that 5-item working memory load engaged such a network during the onset of the delay period, but this activity dissipated as the high-load retention interval continued. The continued persistence of bi-frontal synchronization throughout the delay characterized individuals who's accuracy was below the median performance of the group when no distraction was present during retention. In such cases, task-irrelevant distraction was shown to disrupt this persistent bi-frontal coupling over the course of the delay period and was related to a corresponding increase in DMS performance (Experiment 8). When comparing this low DMS performance group with delay distraction with the high DMS performance group when no distraction was present, the relative time course of bi-frontal theta engagement during delays between these two groups were nearly identical. These results are highly suggestive that the temporal attenuation of this activity over the course of retention, either endogenously or by exogenous distraction, suggests an optimal window of prefrontal engagement that supports delay performance.

Although to determine what form of memory retention is being enhanced could not be addressed in these studies, radiological reports confirm medial temporal lobe damage in the BHS patients of Experiment 6 was confined to the hippocampi bilaterally (see Chapter 4), thus it is unlikely that any hippocampus dependant memory processes can account for distracter facilitated memory enhancement. Furthermore, the corresponding relationship of bi-frontal theta-coupling working memory disruption by distraction and the corresponding DMS behavioural enhancement makes it unlikely that processes dependent upon working memory are responsible. However, since regions of the rhinal cortex are thought to be spared in these patients, one possible explanation is that disrupting faulty maintenance (via interruption of bi-frontal theta-coupling) allows familiarity-based judgements to become unclouded by a noisy working memory representation. Evidence that familiarity-based recognition is dependent on the perirhinal cortex and not on hippocampal integrity support such a notion - *for review see* (Eichenbaum et al., 2007). Therefore, the most parsimonious account is that in cases when stimulus maintenance is faulty, task-irrelevant distraction could then alternatively allow a more accurate familiarity representation to persist that does not rely on working memory resources.

8.2. Closing Summary

We show that actively maintaining configural-relational aspects of a visual scene was associated with theta oscillatory coupling of temporal and occipital visual areas (Chapter 2) and furthermore, that this theta-network is critically dependent on the integrity of the hippocampus (Chapter 5). The ability to support configural-relational forms of working memory are behaviourally shown to depend on hippocampal integrity and cannot be explained by difficulties in perceptual integration (Chapter 4). In contrast, non-configural-relational maintenance was associated with theta synchrony between frontal and parietal regions (Chapter 2) and this form of maintenance was unaffected by hippocampal injury (Chapter 5). Additionally, we establish that unlike maintaining the configural association between objects within a scene, increasing the number of scenes (that is increasing 'load') to be maintained over 5 seconds was associated with a bi-lateral frontal theta synchrony pattern (Chapter 3). Together, these data indicate that hippocampus-dependent theta

synchrony plays an anatomically specific and critical role in for the active maintenance of configural-relational information.

These earlier chapters highlight the functional, behavioural, and anatomical interactions between long-term and short-term working memory and call for a reconsideration of the classical functional-anatomical distinctions between these two forms of memory. By exploring these interactions in later chapters, we find that the longevity of configural-relational DMS representations for short-term maintenance (5-30 seconds) and delayed recognition (45 minutes) seem less apt to decay compared to non-configural-relational DMS. However, both are susceptible to delay interference during maintenance akin to working memory processes. In accordance with these interactions, we find that task-irrelevant distraction during delay periods improved DMS performance in BHS patients. This memory enhancement was robust enough to raise the BHS patients' performance to the same level of college age healthy controls. Additionally, we show that in similar conditions where healthy participants maintain a 'faulty' working memory representation, as in the case of extended delay period lengths, task-irrelevant distraction can increase performance in participants to such an extent that any delay period impairment is abolished. Furthermore we find an electrophysiogical correlate where persistence of visual information is impeded when bi-frontal theta maintenance processes exceed a time dependant optimal efficiency. In such cases, disrupting this coupling mechanism with task-irrelevant distraction allows for a more accurate long-term memory signal to persist, thereby improving performance.

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