The Human Medial Temporal Lobe, Brain Connectivity, and Recognition Memory

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General Abstract

The brain is made up of networks of brain regions that interact through white matter fibre tracts. These pathways are collections of thousands of axons and are vital for the successful functioning of the brain. The recent development of diffusion tensor imaging (DTI) has made it possible to investigate the integrity of these tracts in the human brain, whilst advances in the analysis of functional magnetic resonance imaging (fMRI) data have enabled the functional interaction between brain regions to be assessed. The first aim of this thesis was to investigate one of the main white matter tracts of the medial temporal lobe (MTL), a region of the brain that has been implicated in long-term memory (LTM) functioning. Specifically, the relationship between the microstructural integrity of the fornix, the major efferent of the hippocampus, and recognition memory performance (as assessed by an experimental task) was explored in young adults (Chapter 2). Our results showed that the ability of young adults on recollection, but not familiarity, memory correlated significantly with fornix microstructural integrity. These results speak to theories of MTL function and highlight a role for the hippocampus in recollection. In Chapter 3, it was investigated whether variations in fornix microstructure in young adults are also associated with differences in recall and recognition memory abilities as measured by standard psychometric memory tests. Although aspects of the results from this work converged with those from the first study, an inconsistent pattern of findings was observed overall, perhaps reflecting the relative insensitivity of the standard memory tests used. Next, the consequences of organic brain damage to MTL regions on white matter and resting-state functional connectivity of the brain were investigated in two amnesic patients with focal MTL lesions (Chapter 4). DTI and resting-state fMRI revealed that, compared to age-matched neurologically healthy controls, a patient with gross MTL damage had significant white matter changes in her fornix and right uncinate fasciulus, and also reduced functional connectivity between brain regions associated with the posterior hippocampus resting-state network. Surprisingly, a patient with selective bilateral damage to the hippocampus did not have any significant changes to her resting-state networks or white matter integrity. Finally, a large scale behavioural study was conducted to determine whether a single cognitive training task could be created to improve LTM. This was the first stage of a project designed to determine whether the improvement of LTM via cognitive training is supported by changes in white matter integrity and functional connectivity (Chapter 5). It was found that extensive cognitive training in young adults on a complex spatial working memory task was able to stimulate improvements in recognition memory in some participants. The limitations and

implications of the findings from all of the aforementioned studies are considered in the concluding chapter (Chapter 6).

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Publications

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Chapter 1 - General Introduction

“like waking from a dream….every day is alone in itself…”- Henry Molaison (Milner, Corkin, & Teuber, 1968; p. 217).

Our memories are one of the most important cognitive facilities that we human beings possess. They allow us to acquire, process and store personal experiences. The word ‘memory’ describes a huge array of phenomena and subsequently over the last 200 years many terms have been conceptualized to describe the separate components of memory (these are described below in detail). This thesis will be concerned primarily with long-term memory (LTM) and the functional and anatomical connections that support it. This introductory chapter will provide; (1) an introduction to the taxonomy of memory with a specific focus on LTM, (2) a description of the medial temporal lobe (MTL) and its afferents and efferents and its involvement in memory processes and cognitive abilities beyond the mnemonic and (3) a review of the role of the MTL connections in supporting LTM processes. Finally, a brief overview of the following chapters in this thesis will be given.

1.1. An overview of memory

Memory is a broad concept made up of a number of multiple systems (Aggleton & Brown, 1999; Eichenbaum, Yonelinas, & Ranganath, 2007; Jacoby, 1991; Mishkin, Suzuki, Gadian, & Vargha-Khadem, 1997; Squire & Zola-Morgan, 1991; Tulving, 1983; Tulving & Donaldson, 1972; Vargha-Khadem, 1997). The taxonomy of memory has been extensively investigated for the last 50 years, with psychological and neuroscientific research endeavouring to classify the divisions and the characteristics of the memory systems. All memory systems share similar attributes, for example, they all rely on the acquisition, retention and retrieval of information. On the other hand, they also greatly differ in terms of the type of information acquired, stored, the amount of time it is retained for and the way it influences cognitive and behavioural processes.

These differences will be outlined in the following sections.

1.1.1. Short-term vs Long-term memory

The first divisions described in memory was that of short-term memory (STM) and LTM (e.g. Atkinson & Shiffrin, 1968; Baddeley & Hitch, 1974; Glanzer & Cunitz, 1966; James, 1890; Waugh & Norman, 1965). In this 'multi-store' theory (e.g. Atkinson & Shiffrin, 1968; Peterson, 1966; Waugh & Norman, 1965) stimuli are registered by the appropriate sensory store in a 'preattentive' fashion and are held for a few seconds. If attention is given to the information in the sensory store it transfers to the short-term store, which is characterized by its limited capacity (Broadbent, 1958; Miller, 1956), ability to hold information for around 5-20 seconds, and that information is lost via displacement (Waugh & Norman, 1965). If this information is rehearsed it moves to the long-term store, which has a limitless capacity and the memories there are retained indefinitely (Atkinson & Shiffrin, 1968; Shiffrin & Atkinson, 1969).

1.1.1.1. Perceptual memory

Very briefly, this is the system that allows the storage of sensory information so that it can be perceptually recognized in the future. There are a number of different types of perceptual memory, these include: iconic memory (the very brief (<1000 ms) pre-categorical persistence of a visual sensation), echoic memory (the brief persistence of an auditory sensation) and haptic memory (the brief persistence of touch) as well as verbal and visual STM and LTM.

1.1.1.2. Working memory

STM was later considered better conceptualized as a temporary working memory (WM) store in which information can be manipulated and acted upon in the context of cognitive tasks like reasoning and learning (Atkinson & Shiffrin, 1968; Baddeley, 1986; Baddeley & Hitch, 1974). In their classic experiment, Baddeley and Hitch (1974) depleted the availability of the STM by asking participants to carry out tasks using WM, such as reasoning or prose comprehension, whilst at the same time completing a secondary WM task, like digit span (e.g. learning a sequence of digits). Although carrying out this secondary task did effect the ability to carry out

the first task, the impairment was not catastrophic and it increased as the secondary task load (i.e. length of digit span) was enlarged (Baddeley & Hitch, 1974). This led them to suggest that the STM store is not unitary but consists of a system of interacting components which can perform 2 simultaneous tasks. Their model of WM (Baddeley, 1986; Baddeley & Hitch, 1974) posits that WM is made up of a control system, the central executive, which interacts with two slave storage systems, the visuospatial sketchpad and the phonological loop (see Figure 1-1).

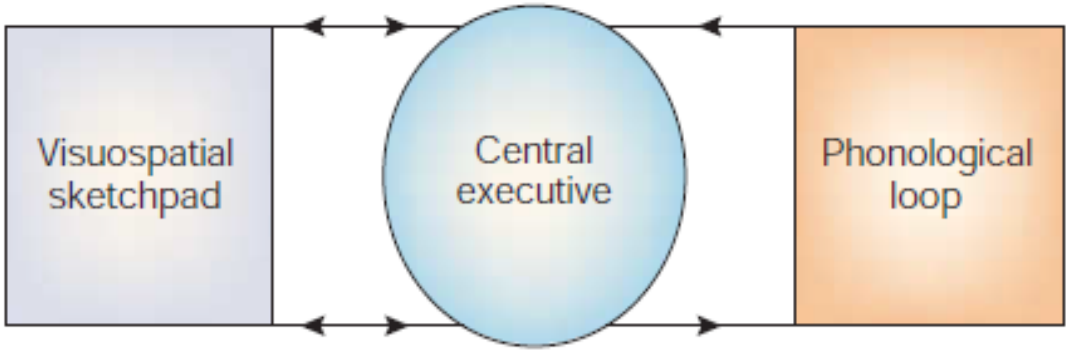

Figure 1-1: A simplified model of Baddeley's working memory model. Adapted from Baddeley (2003).

Baddeley and Hitch's (1974) original framework of WM has proved durable over the last 30 years and is still actively used in studies of cognitive psychology (e.g. Hitch and Logie, 1996) and neuroscience (e.g. Smith and Jonides, 1996, 1997). A number of phenomena, however, do not fit with the original model and a reformulation of the theoretical framework was put forward by Baddeley (2000) with the new addition of the 'episodic buffer'. The episodic buffer (see section 1.1.3 for more information on episodic memory) is thought to provide a bridge between LTM and the phonological loop and visuospatial sketchpad and is controlled by the central executive and therefore, provides an important step between WM and episodic memory through the process of long-term episodic learning (Baddeley, 2000, 2003).

1.1.2. Declarative and Non-declarative Memory

LTM can be further fractionated into declarative and non-declarative memory (see Figure 1-2;

Graf & Schacter, 1985; Squire & Zola-Morgan, 1991). Declarative or explicit memory describes the conscious ability to recover and report on previous events and facts. These memories are acquired relatively quickly and are able to affect our cognitive processes, for example, by allowing us to retrieve an autobiographical memory or a learned fact (Tulving, 1983). Non-declarative memory (also known as implicit, procedural or habit memory) is non-conscious and includes priming, simple classical conditioning and skill and habit learning. These phenomena allow previous events to influence behaviour without being consciously brought to mind (e.g. Heindel, Salmon, Shults, Walicke, & Butters, 1989; Schacter, Chui, & Ochsner, 1993; Squire & Zola-Morgan, 1991). For example, skills like driving a car or riding a bicycle require extensive practice and conscious effort to acquire. Ultimately however, they can become automatic and require little attention to carry out successfully. Declarative memory can be further subdivided into two categories: episodic memory and semantic memory. As this thesis is focused on declarative memory, its key features will be discussed below.

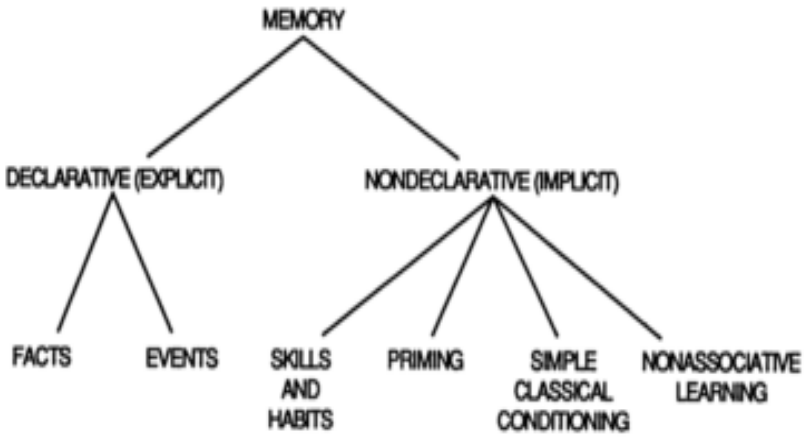

Figure 1-2: The subdivisions of memory. Taken from Squire and Zola-Morgan (1991).

1.1.3. Episodic memory and semantic memory

Tulving and Donaldson (1972) first made the distinction between episodic and semantic memory, and this idea was developed further in 1983 (Tulving, 1983). Episodic memory refers to the ability to consciously recollect previous happenings in a particular place at a particular

time, or put another way: the what, where and when of a memory (e.g. Clayton & Dickinson, 1998; Nyberg et al., 1996; Tulving, 1983; Tulving & Donaldson, 1972). Semantic information, on the other hand, is our ability to learn facts and general knowledge that is not connected to a specific time or place (Tulving, 1985; Tulving & Donaldson, 1972). For example, our ability to know the meaning of words, symbols, concepts, and the relationship between words and objects are all semantic memories. The semantic/episodic distinction was originally thought to be mutually exclusive, although, inevitably these concepts are highly interactive (Graham, Simons, Pratt, Patterson, & Hodges, 2000; Simons, Graham, Galton, Patterson, & Hodges, 2001; Tulving, 1983).

As already described, the focus of this thesis will be long-term episodic memory. One way episodic memory can be assessed is through tests of recognition memory, the ability to recognize previously experienced stimuli. In its most simple form, during a recognition memory task participants are asked to view items in a study phase and then, following a variable delay, a test phase is conducted. In the test phase, items from the study phase (old items) are intermixed with distractors (new items) and participants make old/new decisions about each item they are presented with sequentially. This paradigm therefore allows episodic retrieval to be measured. Our ability to recognize previously presented information was originally thought to be based solely on a 'recollective experience', where the event in the past when it was previously experienced is consciously brought to mind (Tulving, 2002; Tulving & Donaldson, 1972). However, in the 1980 and 90s a number of experiments revealed that recognition is also made up of our ability to 'know' that an item has been seen before, even though we do not explicitly remember it (Gardiner, 1988; Gardiner & Richardson-Klavehn, 2000; Knowlton & Squire, 1995; Rajaram, 1993; Tulving, 1985). It is now widely accepted that recognition is made up of these two constructs, (1) recollection, which is an all-or-none conscious process in which contextual information of the encoding episode is recalled and (2) familiarity or 'the feeling of knowing' which is a fast and automatic process in which no specific details can be recalled about the study event (Mandler, 1980; Tulving, 1985).

The two most common process estimating techniques that sample recollection and familiarity are the Remember/Know (R/K; Tulving, 1985) and the receiver operating characteristic recognition memory tests. Both these tasks are adapted versions of the classic recognition memory test described above. The R/K was first linked to the constructs of recollection and familiarity by Gardiner (1988), who adapted the classic old/new recognition test by asking participants to make judgments about the conscious experience motivating their response. In this way, during the test phase of an R/K, participants are asked to make 3 responses to tests items: "Remember" (R), "Know" (K) or "New" (N). An R response is made if they believe the item was old *and* they can recollect some contextual information from when it was previously seen in the study list; K, if they feel the item was in the study list but cannot recollect its occurrence; and N if they have never seen it before. Although Gardiner (1988) linked R and K responses directly to recollection and familiarity, research suggests that they are not mutually exclusive constructs (Jacoby, 1991; Yonelinas & Jacoby, 1995) and so recollection and familiarity are typically calculated under the assumption of stochastic independence, where the proportion of K responses to old items is divided by the number of opportunities there were to answer K (F= K/(R-1)).

Although the R/K paradigm has been widely utilized to reveal recollection impairment in brain damaged individuals (e.g. Aggleton, Vann, Denby, et al., 2005; Holdstock et al., 2002; Holdstock, Mayes, Gong, Roberts, & Kapur, 2005; Yonelinas et al., 2002) and in neuroimaging paradigms to reveal the neural correlates of recollection and familiarity (e.g. Eldridge, Engel, Zeineh, Bookheimer, & Knowlton, 2005; Gonsalves, Kahn, Curran, Norman, & Wagner, 2005; Henson, Rugg, Shallice, Josephs, & Dolan, 1999) a number of conceptual issues have been recently encountered that call into question the validity of its recollection and familiarity estimates. For example, the construct validity of the R/K has been challenged, with research suggesting R responses do not genuinely represent a qualitatively different kind of memory than the K response (Rotello, Macmillan, Reeder, & Wong, 2005; Rotello & Zeng, 2008; Wais, Mickes, & Wixted, 2008). Indeed, it has been shown that K responses are not necessarily

devoid of contextual information and may involve a small degree of recollection (Wais et al., 2008), whilst the reaction time distributions for the R and K responses are alike, possibly suggesting that they are based on the same information (Rotello & Zeng, 2008).

Another method to assess recollection and familiarity that has become increasingly popular over the past 15 years is the receiver operating characteristic (ROC). ROC recognition memory tests have historically been used in memory research to determine the relationship between mnemonic ability and response bias of old and new decisions (Mandler & Boeck, 1974; Wixted, 2007; Yonelinas, 1994, 2002; Yonelinas & Parks, 2007). At its most basic, an ROC is the proportion of correct recognitions (i.e. the hit rate) plotted against the proportion of incorrect recognitions (i.e. the false alarm rate) across a level of confidence (Yonelinas, 1994). In more detail, during a ROC recognition memory test participants are shown a number of study items sequentially then, following a delay, a test phase takes place where they are shown a mixture of old and new items. As in a classical recognition memory test, they make old and new decisions, but they must rate their decision in terms of confidence. A 6-point scale is often adopted, where 6 represents a high confidence old response in which some specific contextual details, such as a thought or emotion from the study phase, can be recalled. Conversely, 1 represents a high confidence new response (see Figure 1-3 for the ROC scale used in study 2 and 5 presented in this thesis).

To plot a ROC curve the proportion of false alarms (x-axis) are plotted against the proportion of hits (y-axis) cumulatively for the decisions made at the different confidence levels, with the first point representing the most confidently remembered items (hits = P(6|old); false alarms = P(6|new), the second point including these items and the next most confident responses (hits = P(6|old) + P(5|old); false alarms = P(6|new) + P(5|new)) and so on (see Figure 1-4 for an example of an ROC). The ROC curve, therefore, varies from a high confidence response criterion in the lower left hand corner to the lower confidence response criterion in the upper right hand corner.

6 = I remember something specific about the study event

5 = I'm confident/sure it was studied **but** I cannot bring to mind any details about it

4 = I think it was studied, but I'm less confident/sure

3= I think it was **not** studied but I'm even less confident/sure

2= I think it was **not** studied but I'm not confident/sure

1 = I'm confident/sure it was **not** studied

Figure 1-3: ROC recognition memory instructions used in the current thesis to help prompt participants in their ROC confidence judgements.

By asking participants to make confidence judgments about their recognition memory, the processes supporting recognition memory can be studied in a way that the classic old/new or R, K and N decisions do not allow. Analyses of the graphical plots of ROC curves have given rise to parameters which have been used to support two theories that look to explain the processes underlying recognition memory. Firstly, the signal detection theory of recognition memory (Macmillan & Creelman, 2005) posits that recognition memory decisions are made based on the strength of the memory signal in relation to a decision criterion. In this formulation, two Gaussian distributions represent the old and new stimuli presented in the test phase of the recognition memory test with one decision criterion that is participant specific. For a test item to be declared 'old', therefore, the strength of the memory must exceed this criterion. Although an equal-variance detection model have been used in the past, it has been suggested the standard deviation of the old distribution should exceed that of the new item distribution and so an unequal-variance model is quantitatively more accurate (Egan, 1975; Ratcliff, Sheu, & Gronlund, 1992). This theory of declarative memory is known as the unequal variance signal detection model (UVSD; Wixted, 2007). A number of signal detection measurements can be derived by z-transforming ROC data, these include: discriminability, slope of the z-ROC curve and sensitivity (see Chapters 2 and 5). In more detail, discriminability represents the standard bias free measure of recognition memory performance and is calculated using the following

formula (z(P(hits) –z(P(false alarms). The slope of the z-ROC curve, on the other hand, is thought to represent the variance of the encoded and foil items with slope values of 1 representing symmetric ROC curves and values less than 1 represent an asymmetric curve (Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998). It is calculated by transforming all proportion of hits and misses at each confidence level into z space and then measuring the linear regression of this line. Finally, sensitivity is calculated from the slope of the z-transformed ROC data and its y-axis intercept (sensitivity=intercept/POWER(0.5*(1+slope*slope)) and reflects overall accuracy (Macmillan & Creelman, 2005). The UVSD theory indicates that an asymmetric ROC curve, in the top left corner, represents strong memory strength (Figure 1-4 (B), whilst a symmetric one characterizes a weaker memory strength (e.g. Glanzer, Hilford, Kim, & Adams, 1999).

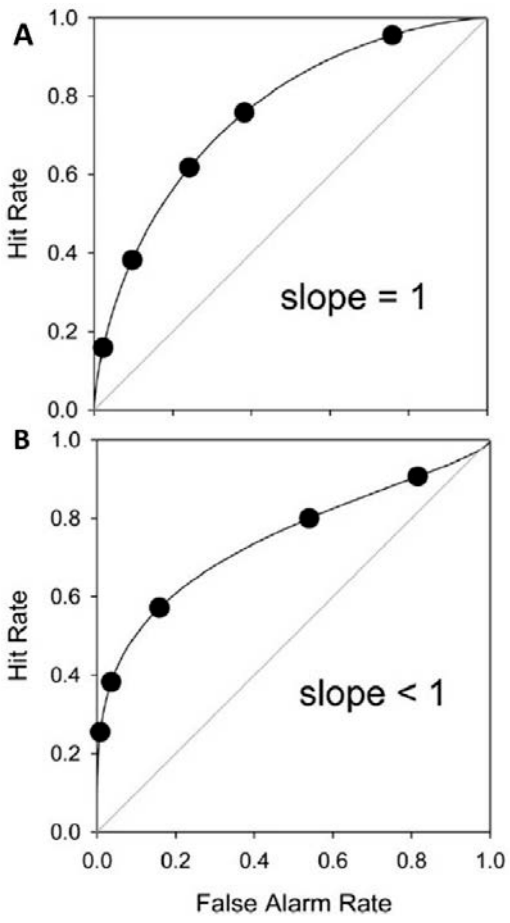

Figure 1-4: Example of a symmetric (A) and asymmetric (B) 6-point ROC curve. Adapted from Wais et al. (2006).

An alternative model posits that recognition judgments are governed by conscious recollection or familiarity, rather than memory strength alone (Yonelinas, 1994). As recollection is assumed to be an all-or-none retrieval process (i.e. a threshold process) it is anticipated that recollected memories lead to highly confident responses (i.e. '6' responses). This is not based on a decision criterion and is a qualitatively different process than familiarity, which is used to make a decision when recollection fails. Familiarity is suggested to be characterized by the equal-variance signal detection theory where confidence is expected to vary based on memory strength and a specific criterion (Yonelinas, 1994). Therefore, according to this model, recognition reflects the independent contributions of both recollection and familiarity, and so is subsequently termed the dual-process signal detection theory (DPSD; Yonelinas, 1994). Yonelinas and colleagues (1998) designed a least-squares method to estimate recollection and familiarity, where the model equation assumes that recognition reflects the independent contribution of each process. The DPSD model estimates recollection and familiarity using the following equations taken from Yonelinas (2001):

$P\ (hits) = R + (1\text{-}R)\ F_{old}$

$P\ (false\ alarm) = F_{new}$

These equations represent that old items which are correctly recognized (hits) can either be recollected (R) or can be judged as familiar (F_{old}) in the absence of recollection (1-R). On the other hand, new items are falsely identified as old (false alarm) when they are familiar (F_{new}). As it is believed that familiarity can be modelled by a signal-detection process, F_{old} and F_{new} will be a function of the distance between the means of the old and new items distributions (d') and the response criterion (c) of the individual and can be represented by the following functions: $F_{old} = \phi\ (d'/2\text{-}c)$ and $F_{new} = \phi\ (-d'/2\text{-}c)$. These represent the proportion of old and new item distributions that exceed the response criterion given that the distance between the means of the two normal distributions in d' (Macmillan & Creelman, 2005). The DPSD theory interprets asymmetric ROC curves as representing recognition memory judgments based on

recollection and familiarity (Figure 1-4 (B), whereas a symmetric curve represents those based on familiarity alone (Figure 1-4 (A); Yonelinas, 1994; Yonelinas et al., 1998; Yonelinas & Parks, 2007).

1.2. Memory and the MTL

1.2.1. Anatomy of the MTL and its connections

Four highly interconnected, but separable MTL structures have been particularly implicated in declarative mnemonic processing: the entorhinal, parahippocampal, and perirhinal cortices and the hippocampus (see Figure 1-5). The hippocampus, consists of the dentate gyrus, subicular complex and the fields CA1-4 and is found at the centre of the MTL encircled by other MTL structures. The parahippocampal cortex is at the posterior extent of the MTL and is rostral to the dorsal visual stream, whilst the perirhinal cortex (PRC; Broadmann areas 35 and 36) is located anterior-medially within the MTL at the junction between the ventral visual stream and the MTL. Finally, the entorhinal cortex (Broadmann areas 28 and 34) is located at the rostral aspect of the MTL and stretches dorsolaterally (Figure 1-5).

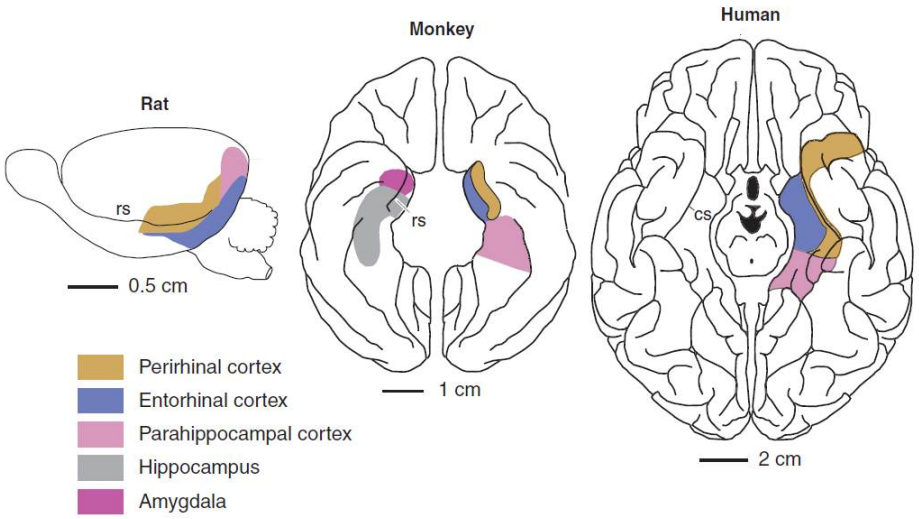

Figure 1-5: Lateral surface of the rat brain (left), ventral surface of the macaque brain (middle) and human (right) with depictions of their MTL structures. In the macaque brain the approximate locations of the hippocampus and the amygdala are represented in grey and magenta respectively on the left hand side of the brain. The entorhinal and PRC boundary is located near the rhinal sulcus (rs) in rats (Burwell, 2001) and in macque's, whilst in the human the PRC is within the collateral sulcus (cs). Note that in rats the parahippocampal cortex is known as the postrhinal cortex. Figure from Murray et al. (2007).

The MTL is a highly interconnected region with a number of fibre pathways creating systems within and beyond the MTL. One of the major white matter tracts of the MTL, that will be the focus of much of this thesis, is the fornix. This tract is the primary efferent of the subicular complex which projects directly to the mammillary bodies (MB) and anterior thalamic nuclei (ATN). Some fibres of the fornix, additionally, directly project from the hippocampus to the prefrontal cortices (Aggleton, 1986; Aggleton, Vann, & Saunders, 2005; Saunders, Mishkin, & Aggleton, 2005; see Figure 1-6). This fibre tract has been suggested to be an important component of the limbic system that allows direct and indirect reciprocal interaction between the hippocampus, medial diencephalon and frontal lobes (see Figure 1-6).

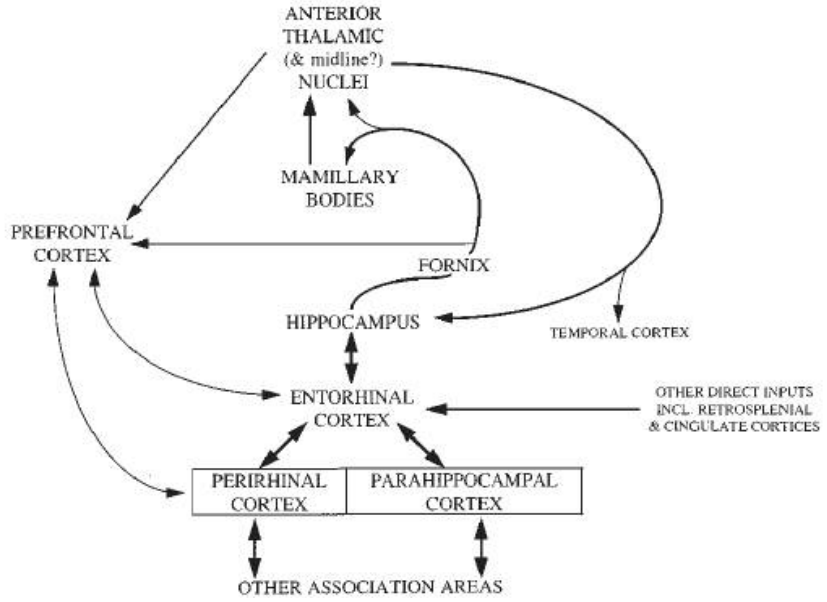

Figure 1-6: A diagram of the principal pathways of the MTL, diencephalon and prefrontal cortex thought to be involved in episodic memory. Taken from Aggleton and Brown (1999).

In terms of its anatomy, the fornix is a large white matter tract in the brain estimated to contain around 2,700,000 fibres in each hemisphere (Daitz, 1953; Daitz & Powell, 1954). It is divided into 3 separate structures: the tails, body and columns (Figure 1-7). In detail: after leaving the subicular complex the fornix fibres accumulate to form the tails at the posterior limit of the hippocampus, underneath the corpus callosum and splenium. They then curve taking a caudal course to the posterior end of the corpus callosum where they join together to become the body. This bundle projects ventrally, curving underneath the corpus callosum until it separates into the two columns at the foramen of Monro. The fornix finally ends as the two columns reach the mammillary bodies (e.g. Bilir et al., 1998; Papez, 1937). The functionality of the hippocampus, MB and ATN and their interactions via the fornix have been extensively investigated due to its hypothesised role in episodic memory (Aggleton, 2008; Aggleton & Brown, 1999, 2006; Aggleton & Pearce, 2001).

As Papez (1937) in his conception of the limbic system revealed, there are a number of additional white matter tracts that allow interaction between MTL regions and cortical and subcortical regions. These include: the cingulum, which allows direct inputs from the cingulate

gyrus to the parahippocampal cortex; the perforant and alvear pathways, which connect the entorhinal cortex to the subiculum of the hippocampus; and the mamillothalamic tract which connects the MB and ATN, and allows indirect hippocampal projections to the ATN (Papez, 1937).

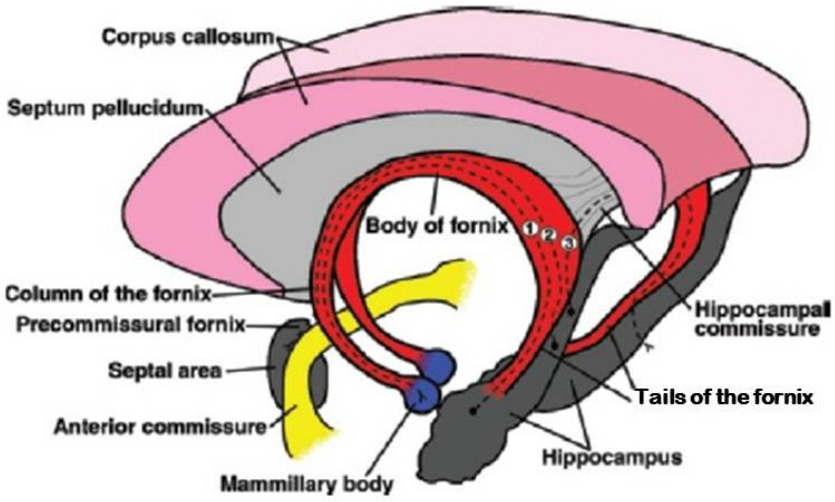

Figure 1-7: Diagram of the tails, body and columns of the fornix in red and its surrounding anatomy. Adapted from Thomas et al. (2011).

Beyond the connections of the MTL, one pathway which has previously received very little attention, despite being one of the largest white matter tracts of the limbic system is the uncinate fasciculus (UF). This tract connects the anterior temporal lobe to the medial and lateral orbitofrontal cortex (Ebeling & Cramon, 1992; Petrides & Pandya, 1988; Ungerleider, Gaffan, & Pelak, 1989). In detail: the UF fibres begin in the temporal lobe medial and anterior to the inferior longitudinal fasciculus before projecting into the external capsule. They then arch forward medially to the insula and laterally to the lenticular nucleus before terminating in the orbitofrontal cortex (see Figure 1-8). The function of this tract is not fully understood (Catani & Thiebaut de Schotten, 2008), although, importantly, it is hypothesised to play a role in the formation and the retrieval of episodic memories (e.g. Nestor et al., 2004; Squire & Zola-Morgan, 1991).

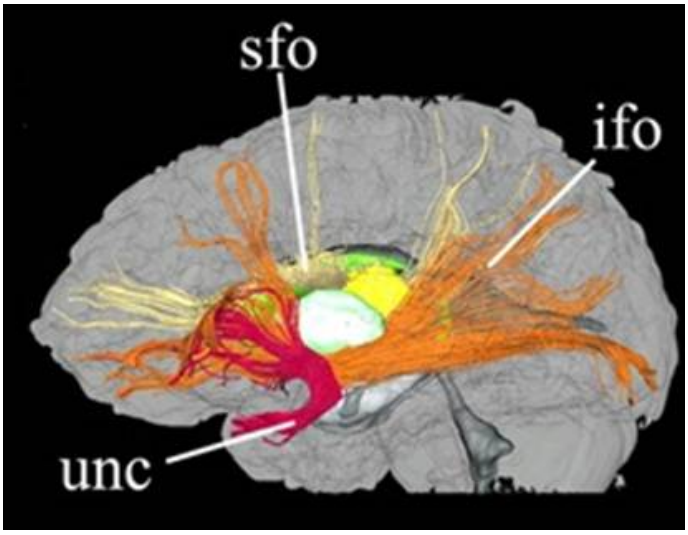

Figure 1-8: 3D depictions of association fibres represented on a 3D white matter atlas created on the basis of high spatial resolution Diffusion Tensor Imaging. Reconstructed fibres are the uncinate fasciulus (unc; pink), the inferior fronto-occipital fasciculus (ifo; orange) and the superior fronto-occipital fasciculus (sfo; beige). Adapted from *Wakana et al. (2003).*

1.2.2. Early MTL lesion research

One of the most famous patients in cognitive neuroscience history is Henry Molaison (known as patient H.M until his death in 2008), who following refractory mesial temporal lobe epilepsy underwent bilateral hippocampal resection. Although the surgery, which removed almost all of his bilateral hippocampi and parahippocampal gyri (including the amygdala and entorhinal cortices) succeeded in controlling his seizures, it resulted in devastating and dense amnesia (Corkin, 2002; Corkin, Amaral, González, Johnson, & Hyman, 1997; Scoville & Milner, 1957; Squire, 2009). Extensive investigations of H.M.'s cognitive abilities conducted over 5 decades showed that he had pervasive LTM deficits regardless of the type of LTM test used (e.g. free recall, yes/no recognition), the type of stimulus used in the task (e.g. digits, faces or sounds), and the sensory modality that the information was presented in (e.g. audition, vision, somatorsensory, olfaction; Corkin, 1984, 2002; Milner et al., 1968). H.M's anterograde amnesia was extensive and he was unable to acquire new episodic memories or semantic knowledge, although his retrograde semantic and episodic memories, apart from the 3 years prior to his

surgery, appeared normal (Scoville & Milner, 1957). Along with these intact retrograde memories, H.M had preserved intellect, WM, perceptual abilities, language and implicit procedural learning (Corkin, 1984; Milner, 1972, 2005; Milner et al., 1968; Scoville & Milner, 1957). For example, Corkin (1968) tested H.M on 3 motor skill tasks - the rotary pursuit, bimanual tracking (which were tested over a number of days) and tapping tasks (which was measured within the same day). On the rotary pursuit and bimanual track H.M.'s performance improved day to day and his tapping times also reduced, indicative of his ability to acquire new motor skills (Corkin, 1968).

These early descriptions of H.M.'s cognitive profile began the modern era of memory research by revealing that, contrary to previously postulations (e.g. Lashley, 1950), LTM functions are separable from all other cognitive functions. Furthermore, his impairments demonstrated the vital role of the MTL structures in declarative memory, whilst indicating that non-declarative memory and WM are likely to be dependent on other neural regions (Corkin, 1984; Milner et al., 1968; Squire & Zola-Morgan, 1991). Since this time, individuals with focal lesions to the MTL and associated amnesia, as a result of anoxia, encephalitis, status epilepticus, cerebral insult or surgery, have been investigated in numerous neuropsychological studies as they provide a valuable opportunity to further elucidate the role of the MTL structures on episodic memory functions (e.g Maguire, Vargha-Khadem, & Mishkin, 2001; Manns & Squire, 1999; McCarthy, Kopelman, & Warrington, 2005; Stefanacci, Buffalo, Schmolck, & Squire, 2000; Vargha-Khadem, 1997).

Although this thesis is concerned primarily with the cognitive neuroscience of LTM in humans, it is worth briefly acknowledging insights provided by animal models of LTM impairment. The human patient findings discussed above have one major limitation in comparison to nonhuman animal work: although it is unlikely that animals and humans experience episodic recall in exactly the same way (Tulving, 1983), research in humans does not allow for controlled focal lesions to specific regions of the MTL and the resulting mnemonic deficits to be elucidated. The most prevalent recognition memory test developed for animals is

the delayed non-match to sample task (DNMS), which is based on the propensity of animals to explore novel stimuli over previously experienced items. Early animal lesion studies using the DNMS revealed that bilateral hippocampal damage results in minor memory impairment (e.g. Weiskrantz, 1971), with later research suggesting that bilateral lesions of additional MTL structures, as well as the hippocampi, are required for severe memory impairment (Mishkin, 1978; Zola-Morgan, Squire, & Ramus, 1994). For example, an evaluation of the behavioural data from 30 monkeys who had undergone MTL lesions concluded that memory impairments were mild when damage was limited to the hippocampus, but these deficits increased as the lesion included the entorhinal and parahippocampus and became very severe if the lesion was further extended to the PRC (Zola-Morgan, Squire, Amaral, & Suzuki, 1989; Zola-Morgan, Squire, Clower, & Rempel-Clower, 1993). These findings led to the theory that severity of memory impairment increases as more components of the MTL become damaged (Zola-Morgan et al., 1994), and the idea that the hippocampus and its surrounding structures form a single MTL system that underlies declarative LTM (see section 1.2.4 for further discussion; Squire, Stark, & Clark, 2004; Squire, Wixted, & Clark, 2007; Squire & Zola-Morgan, 1991). In contrast, other animal lesion investigations have found evidence to support functional segregation in the MTL. For instance, Murray and Mishkin (1998) showed that the hippocampus is not necessary for successful recognition memory in macaque monkeys, whereas Meunier, Bachevalier, Mishkin and Murray (1993) found that PRC lesions alone can impair recognition memory. Furthermore, two recent studies used a modified DNMS on bilateral hippocampal lesion rats to plot ROC curves for the rat's mnemonic performance. They found that rats with damage to their hippocampi had diminished recollection but not familiarity (Fortin, Wright, & Eichenbaum, 2004; Sauvage, Fortin, Owens, Yonelinas, & Eichenbaum, 2008). These findings, along with other nonhuman animal findings (e.g. Farovik, Dupont, Arce, & Eichenbaum, 2008; Sauvage, Beer, Ekovich, Ho, & Eichenbaum, 2010) and the results from amnesic patients and healthy participant neuroimaging work (see next section), support the alternative suggestion that the MTL structures make functionally distinct

contributions towards long-term declarative memory (e.g. Aggleton & Brown, 1999; Bird & Burgess, 2008a; Davachi, 2006; R. A. Diana, Yonelinas, & Ranganath, 2007; Eichenbaum et al., 2007; Montaldi & Mayes, 2010; Ranganath, 2010; Yonelinas, Otten, Shaw, & Rugg, 2005).

1.2.3. The dual-process account of the MTL

Over the past few decades the functional organisation of the MTL in declarative memory has been one of the most controversial research fields in cognitive neuroscience. In keeping with the dual-process view that recognition memory is supported by two distinct cognitive processes (Jacoby, 1991; Mandler, 1980; Tulving, 1985; Yonelinas, 1994), Aggleton and Brown proposed that the hippocampus and PRC are critical for recollection and familiarity respectively (Aggleton & Brown, 1999; Brown & Aggleton, 2001). Some of the first human evidence for this view came from neuropsychological testing of amnesic individuals with focal lesions to the MTL. Using tasks of recall, (that are thought to rely on recollection alone) and recognition (that are thought to rely on both recollection and familiarity) these studies showed that selective bilateral hippocampal lesions patients are impaired on tests of recall, whilst their recognition memory abilities remain preserved (Aggleton & Shaw, 1996; Baddeley, Vargha-Khadem, & Mishkin, 2001; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Vargha-Khadem, 1997, although see Manns & Squire, 1999; Reed & Squire, 1997). When brain damage extends beyond the bilateral hippocampi to its adjacent MTL structures, however, impairment in recall and recognition is observed (Aggleton & Brown, 1999; Aggleton & Shaw, 1996).

To further dissociate the role of the MTL in recognition memory, recognition paradigms that allow recollection and familiarity estimates to be measured separately, such as the R/K and ROC procedures, have been utilized in those with MTL damage. For instance, studies applying the DPSD model have found that hippocampal damage leads to deficits in recollection but not familiarity (Aggleton, Vann, Denby, et al., 2005; Yonelinas et al., 2002, 1998), whilst damage beyond the hippocampus to other MTL structures in particular the PRC, is associated with additional impairment in familiarity (Yonelinas et al., 2002). These findings are supported by

behavioural testing of patient N.B., who has unique focal damage to the left PRC, but preserved bilateral hippocampi following left anterior temporal lobe resection for intractable epilepsy (Bowles et al., 2007). Her performance on recognition memory tests including the R/K and an ROC, showed that she exhibits a persistent impairment in familiarity, but intact recollection memory (Bowles et al., 2007). This study is significant as it is one of the only human cases where damage is restricted to the PRC. When combined with knowledge obtained from the selective hippocampal lesion studies, it therefore allows a double dissociation between memory processes and MTL structure to be observed.

Since patients with circumscribed MTL damage are rare, the advent of neuroimaging, particularly functional magnetic resonance imaging (fMRI), has provided an excellent opportunity to further investigate the role of the MTL structures in long-term declarative memory encoding and retrieval. fMRI investigations interested in the encoding of recognition memories typically use the subsequent memory paradigm. In one variation of this procedure designed to investigate the neural correlates of recollection and familiarity, participants are asked to study items in two different conditions (e.g. words in red or green print) inside the scanner and then to take a surprise recognition memory test (e.g. of words presented in black) outside the scanner. If an item is considered 'old' then the participant is asked to make a source memory judgement (i.e. was the word presented in red or green in the scanner?). The dual-process theory interprets correct item and source memory judgment to reflect a recollection-based decision, whereas old responses with correct item but incorrect source decisions are believed to be based on familiarity. Based on their responses on the recognition memory test, the participants' brain activity during encoding for items that were subsequently recollected, familiar or forgotten can be examined. Retrieval studies conversely scan participants as they carry out recognition memory tests that allow the separation of recollection and familiarity processes, such as the ROC and R/K procedures.

Early fMRI studies confirmed that the MTL plays an important role in declarative long-term memory encoding (e.g. Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Wagner et al.,

1998) and retrieval (e.g. Daselaar et al., 2001; Donaldson, Petersen, Ollinger, & Buckner, 2001). A number of fMRI studies have since investigated the role of the MTL structures in recollection and familiarity encoding using the subsequent memory paradigm. For example, Davachi, Mitchell and Wagner (2003), asked participants to view adjectives in the scanner and to read them backwards or mentally imagine a spatial scene associated with them. Following scanning a subsequent recognition memory test for the studied words assessed if each word was remembered (item) and if so, whether it was seen in the 'read backwards' or 'imagine' condition (source). Results showed that hippocampus and posterior parahippocampal cortex activity at encoding predicted later source recollection, but not item recognition, whilst encoding activity in the PRC predicted later item recognition, but not subsequent source recollection (Davachi et al., 2003). These findings were further extended by a study by Ranganath et al. (2004) that also carried out a subsequent memory paradigm using words, but asked participants to indicate 1-6 confidence ratings on their old/new decisions during the recognition memory test. Their findings replicated those of Davachi et al. (2003) and critically, were consistent with the predictions of the DPSD (Yonelinas, 1994) - there was a linear relationship between rhinal cortex activity and confidence for recognized items, but not the recollected source memory items (Ranganath et al., 2004). These data, therefore, support the idea that familiarity is based on a graded memory strength signal (Yonelinas, 1994).

In terms of retrieval studies, in agreement with those mentioned above, source memory effects (recollection) are associated with positive activation in the hippocampus and posterior parahippocampal gyrus (e.g. Cansino, Maquet, Dolan, & Rugg, 2002; Dobbins, Foley, Schacter, & Wagner, 2002). On the other hand, the neural signature for item memory at retrieval is usually a decrease in activity in the PRC (e.g. Henson, Cansino, Herron, Robb, & Rugg, 2003). For example, Montaldi, Spencer, Roberts and Mayes (2006) scanned participants as they carried out a recognition memory test for everyday scenes and made judgments if they thought the item was familiar using a 3-point confidence scale (high, medium and low), recollected or new. A parametric analysis showed that as familiarity confidence increased the

activity in the PRC and surrounding areas (insula, left superior temporal cortex) declined in a linear fashion. Hippocampal activity, however, was not modulated linearly or quadratically by familiarity memory strength and was activated in response to recollection retrieval (recollection-strong familiarity) (Montaldi et al., 2006). This study is significant, therefore, as it matched for memory strength between recollection and high confidence familiarity and still showed that recollection only activated the hippocampus (see next section for further discussion on the potential confounds between memory strength and recollection/familiarity). A similar linear decrease in PRC activity in association with increasing familiarity confidence has also been observed by Daselaar, Fleck and Cabeza (2006), and there are two potential explanations for this effect, which are not necessarily mutually exclusive of one another. First, the PRC may support item familiarity memory via repetition suppression of neural firing. Indeed, this is consistent with nonhuman animal electrophysiological studies that demonstrate a decrease in PRC neuron firing when a stimulus is repeated (e.g. Brown & Xiang, 1998). Second, the PRC may be preferentially encoding novel items during the recognition memory test phase (Henson et al., 2003), leading to relatively lower levels of activity for the familiar items.

1.2.4. The unitary/memory strength account of the MTL

In contrast to the dual-process view, others argue that there is no functional specialisation within the MTL and that this region forms a single unitary system that supports the acquisition of new declarative LTM (Squire et al., 2004, 2007; Squire & Zola-Morgan, 1991). This 'unitary account' predicts that all MTL structures contribute to memory and therefore, a relationship should be observable between the extent of MTL damage and amount of EM loss (Squire et al., 2004; Zola-Morgan et al., 1994). The first evidence for this theory came from early human lesion studies that found that patients with lesions encompassing the hippocampus and addition MTL regions (e.g. patient H.M.; Corkin et al., 1997) had more severe LTM impairments than those with lesions circumscribed to the hippocampus alone (e.g. patients G.D., L.M and R.B.; Rempel-Clower, Zola, Squire, & Amaral, 1996; Zola-Morgan, Squire, & Amaral, 1986).

Critically, these findings were supported by convergent work in nonhuman primates (see section 1.2.2), which demonstrated that there was a positive relationship between lesion size and mnemonic deficit (e.g. Zola-Morgan et al., 1989, 1993).

Squire et al. (2004, 2007) has recently emphasized that the unitary account does not imply that the MTL structures perform a homogenous functional contribution toward declarative memory, but rather, that they all contribute in an equal fashion. Thus, all regions of the MTL are hypothesized to play an equal role in the processes of recollection and familiarity (Squire et al., 2004, 2007). Neuropsychological evidence for this suggestion comes from studies that have demonstrated that amnesic patients with bilateral hippocampal lesions display deficits on tests of recall and recognition (Kirwan, Wixted, & Squire, 2010; Kopelman et al., 2007; Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Manns & Squire, 1999; Reed & Squire, 1997; Wais, Wixted, Hopkins, & Squire, 2006; Wixted & Squire, 2004). For example, a group of 7 patients with circumscribed bilateral hippocampus damage were tested using 3 standard tests and one experimental test of recall and/or recognition memory: (1) the Warrington recognition memory test (Warrington, 1984) with an adapted 24 hour delay; (2) the Doors and People Test (Baddeley, Emslie, & Nimmo-Smith, 2006); (3) the Rey Auditory Verbal Learning Test (Meyers & Meyers, 1995); and (4) a R/K recognition task (Manns et al., 2003). The patients were similarly impaired on all tasks, including the R and K components of the experimental task, suggesting that the hippocampus is important for both recall/recollection *and* recognition/familiarity (Manns et al., 2003).

With regards to the use of ROCs in recognition memory testing in MTL lesion patients, proponents of the unitary view suggest that the specific recollection deficits reported in hippocampal lesion patients (i.e. a symmetric ROC; Aggleton, Vann, Denby, et al., 2005; Yonelinas et al., 2002) do not reflect a qualitative difference in their recognition memory decisions but, rather, a quantitative one (Squire et al., 2004, 2007; Wais et al., 2006). More specifically, since memory impaired patients have weaker memories than controls, they often exhibit impairments in recollective memory, which are dependent on strong memory strength.

According to this view, therefore, recognition memory performance can be characterised by a single process UVSD model (see earlier section 1.1.3). In support of this, Wais and colleagues (2006) used a ROC recognition memory test to assess the recognition memory of 6 patients with selective bilateral hippocampal damage and age-matched controls. Critically, when comparing the hippocampal lesion patients and their controls, they 'matched' memory strength between the two participant groups by asking the patients to carry out 2 ROC recognition tests: one where the study phase consisted of 10-items followed by a test phase that was repeated 4 times (H-10), and another where the study phase consisted of 50 items (H-50) and a test phase. The age-matched controls only received the 50 item ROC recognition memory test (C-50). Thus, memory strength was equated between controls and patients in the H-10 and C-50 conditions and this was reflected by their comparable d' scores on these tasks. Crucially, when each groups mean ROC was analysed, no significant differences were observed between the patient (H-10) and control (C-50) slope parameters or recollection and familiarity estimates. These data were taken to suggest that, in line with the UVSD model, hippocampal damage results in quantitative reductions in memory strength and not qualitative changes in recollection or familiarity ability (Wais et al., 2006).

Convergent evidence for the unitary/memory strength account of MTL function comes from fMRI studies of healthy individuals as they conduct recognition memory paradigms (Gold et al., 2006; Kirwan, Wixted, & Squire, 2008; Shrager, Kirwan, & Squire, 2008). As described previously when discussing the dual-process account, these studies commonly use subsequent memory paradigms where participants encode items within the scanner in different contexts and then make item and source memory judgements in a surprise recognition memory test outside the scanner. The unitary model predicts that the primary difference between 'old' responses where there is a correct item and source memory judgment and those when only the item judgement is correct, is a change in the strength of the memory. Additionally, this account argues that all MTL regions contribute towards item and source memory judgements to a similar degree (Gold et al., 2006; Shrager et al., 2008). Kirwan and colleagues (2008) asked

participants to study words in red or green whilst in the scanner and then administered a surprise ROC recognition memory test with a source memory judgment, where both the item response and the source memory judgement were rated in confidence on a 1-6 point scale. A subsequent memory analysis of the fMRI encoding data for these items employed a novel technique that allowed the investigators to evaluate the effect of item memory strength independently from the effect of source memory (recollection) and vice versa. For item memory (familiarity) this was achieved by only analysing trials in which participants rated an item as old (confidence levels 4-6), but then went on to rate their source memory judgement as a guess (confidence rating 3-4). Using this approach, regions within the hippocampus and PRC were found to vary as a function of item memory strength alone. On the other hand, a linear trend analysis for source memory (i.e. high (6), medium (5) and low (4) confidence) was conducted where item memory was held constant at a high confidence level (i.e. at confidence level 6). This analysis revealed regions in the prefrontal cortex (PFC) were activated as function of source memory strength, when item memory strength was held constant. These findings suggest that the MTL regions are recruited in a manner that is predictive of subsequent item memory strength, and that the PFC is the primary cortical region associated with conscious recollective retrieval (Kirwan et al., 2008).

1.2.5. Resolving the DPSD vs. UVSD debate

As seen above, there are a number of findings in support of either a unitary or dual-process account of MTL function. It is important to note, however, that much of this divergent data may be accounted for, at least in part, by methodological issues. For example, with regards to the fMRI studies, differences may arise due to difficulties in determining the exact location of significant activations within the MTL structures, which are relatively small in size and are located within close proximity to each other. What is more, the MTL structures, in particular the hippocampi and the PRC are vulnerable to MRI signal distortion and loss due to nearby air/tissue and bone/tissues junctions causing local magnetic field distortion (Olman, Davachi, & Inati, 2009). Similarly, the differences between the MTL lesion patient findings could be

explained partially by the limitations associated with this experimental approach. Firstly, as individuals with circumscribed MTL damage are so rare, many studies are based on a single-case or small group approach, which could lead to problems with statistical sensitivity. In addition, there may be individual differences between the patients not only in the extent and the exact location of the MTL damage (which may not be obvious from structural MRI scans) but also with regards to their profiles of cognitive impairment (Holdstock et al., 2008). Finally, considering the brain is comprised of multiple, heavily inter-connected structural and functional networks, many of the cognitive deficits observed following MTL lesion damage may actually be the result of negative knock-on effects in regions/connections beyond the MTL. Despite these methodological considerations, one may note, however, that there appears to be a predominant amount of data in support of a dual-process, rather than unitary, understanding of the MTL. For instance, in the realm of functional neuroimaging studies there are now over 22 studies that show that source memory is associated with hippocampus activations, and 13 that demonstrate that the anterior parahippocampal gyrus, including the PRC, are active during item memory (Diana et al., 2007).

It is important to consider that the dual-process and unitary views may not fully capture the role of the MTL structures in episodic LTM. Indeed, a number of more recent accounts of MTL function in declarative memory/recognition memory may be able to reconcile many of the disparate findings in the literature (e.g. Davachi, 2006; Eichenbaum et al., 2007; Mayes, Montaldi, & Migo, 2007; Ranganath, 2010). Although it is not possible to discuss all of these within the scope of this chapter, two of these models with particular relevance to the recollection-familiarity debate, will be described in brief. The binding of item and context (BIC) model put forth by Ranganath and colleagues (Diana et al., 2007; Ranganath, 2010), suggests that recollection and familiarity cannot be mapped simply onto distinct MTL regions and that the type of information involved also needs to be taken into account. Drawing on animal studies and the anatomical connectivity of the MTL, their model suggests that the PRC processes detailed information about the specific items to be remembered, and the

parahippocampal cortex processes information about the context, both spatial and non-spatial, in which an item is encountered. This information about the 'what' and 'where' is then bound together in the hippocampus which creates item-context associations. This account would, therefore, predict that item representations, which are encoded in the PRC, are able to support familiarity because no contextual information is necessary to make this judgment. In contrast, the hippocampus is crucial for recollection decisions since these require contextual information and item-context associations to be retrieved. Where the BIC model extends the original dual process view is that it also suggests that the parahippocampal cortex is also important for the recollection process as it encodes contextual information (Diana et al., 2007). Support for this idea comes from fMRI studies that show that the posterior parahippocampal cortex is active during the processing of spatial and non-spatial contextual information (e.g. Aminoff, Gronau, & Bar, 2007; Bar, Aminoff, & Schacter, 2008). In addition to this, the BIC model argues that the PRC *can* support source memory if the items and their associations are processed as a single unit (i.e. are unitized; Diana, Yonelinas, & Ranganath, 2008; Haskins, Yonelinas, Quamme, & Ranganath, 2008; Mayes et al., 2007) or when the source information is encoded as an item feature (Diana, Yonelinas, & Ranganath, 2009; Staresina & Davachi, 2006). To support this, MTL lesioned patients exhibit milder recognition impairments when they study word pairs under a condition that encourages them to be unitised in comparison to when they try to encode the two words separately (Quamme, Yonelinas, & Norman, 2007).

An additional account of MTL function is termed the Convergence, Recollection, and Familiarity Theory (CRAFT; Montaldi & Mayes, 2010; see the Domain Dichotomy view; Mayes et al., 2004, 2007). Similar to the BIC model, this viewpoint posits that the PRC binds object information to form new object/item associations, the parahippocampal cortex binds converging contextual information and the hippocampus binds together object and context information, to form new object-context associations (Montaldi & Mayes, 2010). In contrast to the BIC model, however, the CRAFT does not predict that the parahippocampal cortex can support recollection. This is because the cytoarchitecture of the parahippocampal cortex is

suggested to lead to poor rapid pattern separation, which provides inflexible associative processing of context components that are subsequently only able to support familiarity but not recollection (Montaldi & Mayes, 2010). Evidence for this idea has yet to be formally tested but the authors suggest future investigations that would elucidate the role of the parahippocampal cortex in familiarity and/or recollection. For example, in rodents the effect of postrhinal lesions on tasks where context recognition and recall of associations involving context could be conducted.

1.3. Beyond Recognition memory in the MTL structures

1.3.1. Working Memory and the MTL

Although the MTL has been historically thought to be the primary site of declarative LTM formation, there has been an increasing amount of evidence to suggest that this region may also play a role in cognitive functions beyond the long-term domain. As mentioned previously, MTL damage is traditionally thought to preserve WM but impair LTM (Squire et al., 2004, 2007). Notably, however, the stimuli that have typically been used to assess WM in neuropsychological tests, such as digit span, have often been easy to verbalise. Individuals with MTL lesions do exhibit WM deficits on such tasks, when words (Baddeley & Warrington, 1970) or numbers (Cave & Squire, 1992) are used. Crucially, however, evidence has recently emerged to suggest that these patients do, in fact, show WM deficits when certain types of visual stimuli are used, such as scene, faces and objects. These findings have led to the proposal that, under certain circumstances, the MTL structures may play an important role in WM (Fuster, 1997; Nairne, 2002; Ranganath & Blumenfeld, 2005).

One of the first studies to suggest a critical role for the MTL in WM found that MTL lesion patients had difficulties retaining novel visual objects over a number of seconds in a delayed-match-to-sample task (Holdstock, Shaw, & Aggleton, 1995). These findings were corroborated and extended in the same year when it was shown that MTL lesion patients not only had impairments in novel object WM tasks, but also a spatial WM test (Owen, Sahakian,

Polkey, & Robbins, 1995). Since these early findings, a number of studies have emerged demonstrating that MTL lesion patients, including those with selective bilateral hippocampal lesions, have deficits in WM tasks involving visual stimuli (Hannula, Tranel, & Cohen, 2006; Hartley et al., 2007; Olson, Moore, Stark, & Chatterjee, 2006; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006). For example, Hartley et al. (2007) tested 4 bilateral hippocampal lesion individuals and 1 patient with more extensive damage encompassing the parahippocampal gyrus on a 2 second delayed-match-to-sample test of WM and a match-to-sample test of perception using topographic scenes. Novelly, patients were asked to differentially observe either the topography or non-spatial aspects of the same visual scenes. For example, in the non-spatial condition participants were required to remember or match the correct image based solely on non-spatial features in the scene (i.e. lighting, cloud cover, vegetation), whilst in the spatial condition participants had identifed the correct image based on its topographic features (i.e. the size, number and placement of hills). Results showed all patients were impaired on the topographic WM task but their ability on the non-spatial WM and perception tests were spared. Perception for scenes however was grossly impaired in the patient with parahippocampal damage, mildly impaired in two hippocampal cases and preserved in the other 2 hippocampal patients. In addition to this, impairments on WM tasks involving unfamiliar face stimuli have also been found in MTL lesion patients (Ezzyat & Olson, 2008; E. A. Nichols, Kao, Verfaellie, & Gabrieli, 2006; Olson, Moore, et al., 2006). Olson and colleagues (2006) reported that 3 MTL damage individuals showed deficits on spatial, face and colour WM tasks even at a delay of 4 seconds (Olson, Moore, et al., 2006). It is possible that MTL lesion patients have difficulties with visual but not verbal WM tasks because visual stimuli are difficult to create verbal rehearsal strategies for during the delay (Olson, Moore, et al., 2006). Moreover, it may be that specific attributes of the stimuli are particularly difficult for MTL patients to perceptually process, leading to mnemonic impairments (this will be discussed in detail in the next section).

Converging with these patient findings, fMRI neuroimaging investigations have also

revealed hippocampal, parahippocampal, entorhinal and perirhinal activity during WM paradigms using faces (E. A. Nichols et al., 2006; Ranganath & Esposito, 2001; Rissman, Gazzaley, & D'Esposito, 2008), scenes (Lee & Rudebeck, 2010a; Stern, Sherman, Kirchhoff, & Hasselmo, 2001; Toepper et al., 2010) and objects (Ranganath, Cohen, & Brozinsky, 2005). Stern and colleagues (2001) scanned participants as they carried out a 2-back WM task using novel (i.e. presented once during scanning) and highly familiar (i.e. presented to participants 14 times before scanning) complex pictures. Results showed MTL regions were active during the N-back task for novel complex pictures, whilst the PFC was associated with the monitoring of the highly familiar complex pictures. The authors concluded the MTL is recruited for the short-term manipulation of information when there is no prior representation in the brain, whilst the PFC is important for monitoring familiar stimuli (Stern et al., 2001). In addition, Ranganath and D'Esposito (2001) scanned participants as they alternately carried out a WM, LTM encoding tasks and LTM retrieval task of novel faces. Activity in the bilateral hippocampus was observed during the WM but neither LTM conditions, whereas parahippocampal activity was associated with both LTM but not the WM conditions. Taken together these findings suggest the MTL regions are active during WM tasks if the stimuli presented are novel to the participant.

Based on the aforementioned findings, recent arguments against the neural distinction between WM and EM have been made (Ranganath & Blumenfeld, 2005; see however Jeneson & Squire, 2012) for a recent rebuttal of this view), consistent with a number of unitary store models that propose that EM and WM are not supported by separable neuronal regions, but by the same neocortical memory network that can either be reactivated in response to external stimuli or top-down signals for memory retrieval (Fuster, 1997; Nairne, 2002).

1.3.2. Representational accounts of MTL function

Extending beyond the domain of WM, there is now also considerable evidence that the MTL structures may be critical for higher order perceptual processes. According to this view, MTL regions play specific roles in the processing of visual stimuli, with the hippocampus associated

with processing spatial stimuli and the PRC associated with processing object stimuli (Baxter, 2009; Bird & Burgess, 2008a; Bussey, Saksida, & Murray, 2005; Graham, Barense, & Lee, 2010; Lee, Yeung, & Barense, 2012; Murray & Bussey, 1999). This account suggests that the hippocampus and PRC are not involved in any specific mnemonic process *per se* (e.g. recollection vs. familiarity; LTM vs. STM; declarative vs. non-declarative) but rather, that their involvement in memory processing is dictated by the type of information (e.g. scenes vs. objects) to be remembered.

1.3.2.1. Evidence from nonhuman animal studies

The foundation of a representational understanding of MTL function comes from early lesion and electrophysiological studies conducted in rats and monkeys. With regards to a role for the PRC in higher-order object perception, one investigation observed that monkeys with PRC lesions had deficits in a zero-delay object match-to-sample task and in making discriminations between objects presented simultaneously (Eacott, Gaffan, & Murray, 1994). This result was further supported by findings that monkeys with PRC ablations have impairments discriminating between simultaneously presented objects that share a high number of visual features (i.e. high feature ambiguity) or when they are presented from different viewpoints (Bartko, Winters, Cowell, Saksida, & Bussey, 2007; Buckley, Booth, Rolls, & Gaffan, 2001; Bussey, Saksida, & Murray, 2002). These findings (in addition to those from studies in humans described below) led to a theoretical conceptualisation of the functional contribution of the PRC, termed the representation-hierarchical model (Bussey et al., 2005; Murray & Bussey, 1999; Murray, Bussey, & Saksida, 2007; Saksida & Bussey, 2010). This account proposes that the PRC forms representations of complex conjunctions of stimulus features (Bussey et al., 2002; Murray & Bussey, 1999) and therefore, acts as an extension of the representational hierarchy in the ventral visual stream (Ungerleider & Mishkin, 1982). Subsequently, lesions to this area can result in impairment in tasks that place a significant demand on high-level conjunctive representations of features.

The hippocampus has been known to play an important role in spatial cognition for over 40 years. O'Keefe and Dostrovsky (1971) discovered hippocampal neurons in rats, which they named 'place cells', that only fire when the rodents are in a specific location. These 'place cells' form context-dependent maps (O'Keefe & Nadel, 1978) which can remain established for a number of weeks and have been suggested to be capable of supporting LTM (Lever, Wills, Cacucci, Burgess, & O'Keefe, 2002). Electrophysiological data has also revealed that activity in the hippocampus is highly sensitive to changes in spatial environment, item-in-location associations and the spatial arrays of items (Eichenbaum, 2004; O'Keefe, 1976; O'Keefe, Burggren, Donnett, Jeffery, & Maguire, 1998; O'Keefe & Nadel, 1978). Lesions to the hippocampus and its major efferent tract, the fornix, can also lead to severe impairments in spatial tasks in macaques (e.g. D. Gaffan & Harrison, 1989a; Hampton, Hampstead, & Murray, 2004; Murray, Baxter, & Gaffan, 1998) and in rats (e.g. Aggleton, 1986; Morris, Garrud, Rawlins, & O'Keefe, 1982), whereas hippocampal lesions in monkeys often leave memory intact when they are non-spatial in nature (e.g. Murray, Gaffan, & Mishkin, 1993; Murray & Mishkin, 1998) (see however, Brasted, Bussey, Murray, & Wise, 2003). Although the majority of these findings are in the context of mnemonic paradigms (i.e. relying on the encoding and retrieval of information), it has been postulated that the hippocampus may be crucial in the higher-order perception of scenes (D. Gaffan, 2001, 2002). Indeed, a number of studies from humans have recently provide strong support for this view (see following sections; Lee, Yeung, et al., 2012).

1.3.2.2. Evidence from human amnesia

The idea that the hippocampus and PRC are regions concerned with the perceptual processing of scenes and objects respectively has been supported by a number of behavioural studies conducted in patients with MTL lesions. Lee and colleagues, (Lee, Buckley, et al., 2005; Lee, Bussey, et al., 2005; Lee, Buckley, et al., 2006) explored the role of the MTL in higher-order perception through a series of experiments designed to tax the perception of complex scene and object/face stimuli. One paradigm that has been used is the oddity judgement task, in which participants are instructed to choose the odd-one-out from an array of simultaneously

presented stimuli. Crucially, all the information required to solve any given trial is always available to the participant and thus, this task does not place an explicit demand on mnemonic processing. In one study, individuals with circumscribed hippocampal lesions and those with gross MTL lesions encompassing both the hippocampus and the PRC, performed oddity judgements for 3D virtual reality scenes and photographs of unknown faces (Lee, Buckley, et al., 2005). To manipulate the level of perceptual processing, two conditions were included per stimuli; one where the viewpoint of the stimuli was the same ('same view'); and a second in which the viewpoint was different ('different views'; e.g. see Figure 1-9). The performance of both patient groups was comparable to healthy controls in the same view conditions. Those with selective hippocampal lesions had impairments, however, when making odd-one-out judgements for scenes shown from different views and intact performance for different views faces (Lee, Buckley, et al., 2005). In contrast, the patients with damage extending beyond the hippocampus to the PRC had significant deficits in both faces and scene different views conditions.

The same oddity paradigm was conducted on patients with Alzheimer's disease (AD) and semantic dementia (SD) (Lee, Buckley, et al., 2006), which in their early stages of progression are associated with predominant hippocampal and PRC atrophy, respectively (Davies, Graham, Xuereb, Williams, & Hodges, 2004; Du et al., 2001; Jack et al., 1999). It was found that AD patients had impairments on different views scenes but not faces stimuli whereas SD patients had intact different views scene discrimination but significant difficulties with faces presented in different views (Lee, Buckley, et al., 2006). Taken together, these findings provide evidence from humans that the hippocampus is crucial for complex scene perceptual judgements (Graham et al., 2010; Lee, Barense, & Graham, 2005; Lee, Yeung, et al., 2012) and the PRC is critical for processing complex objects.

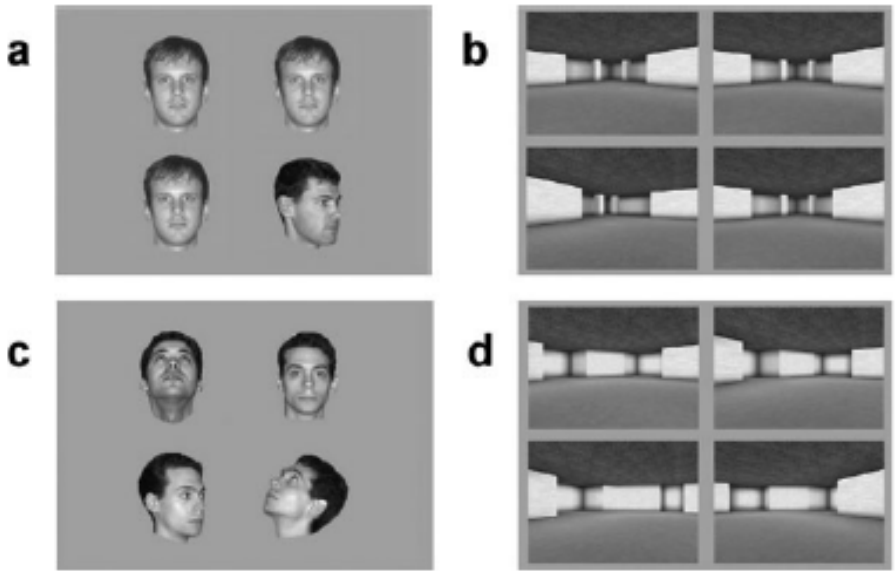

Figure 1-9: Example trails from the oddity task for the conditions (a) same view face, (b) same view scene, (c) different view face, (d) different view scene used in Lee et al., (2005a, 2006). In each trail the participants made odd-one-out decisions. All stimuli were trial unique. Adapted from Lee et al. (2005b).

Additional support from human amnesic patients for a role for the PRC in higher-order perception comes from a number of studies by Barense and colleagues (Barense et al., 2005; Barense, Gaffan, & Graham, 2007; Barense, Ngo, Hung, & Peterson, 2011; Barense, Rogers, Bussey, Saksida, & Graham, 2010). In one study hippocampal lesion patients and gross MTL damage patients (including damage to the PRC) were assessed on a series of trial-unique oddity tasks using different types of object and simple visual stimuli: (1) novel objects (i.e. greebles and fribbles; Gauthier & Tarr, 1997; Williams & Simons, 2000); (2) familiar objects (e.g. cars and plants); (3) different sized squares; and (4) different coloured squares. The novel and familiar objects were further manipulated so that the degree of overlapping features (i.e. feature ambiguity) was controlled and ranged from small, intermediate to large for the fribbles, and low and high for all other objects. Results showed that all patients performed in the normal range when the stimuli shared few features in common (i.e. low feature ambiguity). However, when the objects had a large number of features in common (i.e. high feature ambiguity) and

subsequently object processing demands were high, patients with PRC lesions showed a significant impairment (Barense et al., 2007). This finding was replicated in patients with SD (Barense, Rogers, et al., 2010) and further investigations have also revealed that PRC lesion patients demonstrate impairments in complex object processing even when only single objects are presented (Barense et al., 2011; Lee & Rudebeck, 2010b). Cumulatively, the aforementioned evidence has provided strong support for the notion that the human PRC, similar to the monkey PRC, is critical for higher-order object perception (Graham et al., 2010) (see however, S. Kim et al., 2011; Knutson, Hopkins, & Squire, 2012; Levy, Shrager, & Squire, 2005; Shrager, Gold, Hopkins, & Squire, 2006, for contradictory evidence).

1.3.2.3. Evidence from functional neuroimaging

Further evidence for a representational understanding of the MTL comes from fMRI neuroimaging studies of healthy individuals. When completed in the scanner by neurological healthy individuals, different views scene oddity judgement is associated with significant posterior hippocampus activity (Barense, Henson, Lee, & Graham, 2010; Lee, Scahill, & Graham, 2008), whilst complex object and face discriminations are associated with PRC activity (Barense, Henson, et al., 2010; Lee, Bandelow, Schwarzbauer, Henson, & Graham, 2006; Lee et al., 2008; O'Neil, Cate, & Köhler, 2009). Kim et al. (2011), however, recently proposed that successful scene oddity judgments may be dependent on successful incidental LTM encoding and thus, MTL activity during this task may, in fact, reflect mnemonic processing. To speak to this, a novel study recently aimed to dissociate the role of the hippocampus in scene perception and spatial LTM by using multivariate pattern analysis (MVPA) to decode the distributed neural representations associated with each process (Lee, Brodersen, & Rudebeck, 2012). Healthy participants were scanned using fMRI during a different views scene oddity judgement task and were then given a surprise recognition memory test outside the scanner for the oddity trials shown during scanning. This allowed each trial to be categorised in terms of oddity judgment accuracy and subsequent memory. Univariate analysis revealed hippocampal activity was associated with correct oddity judgments and crucially, MVPA was

able to predict correct from incorrect oddity trial on the basis of the voxels within the hippocampus, irrespective of subsequent memory performance (Lee, Brodersen, et al., 2012). These findings contradict Kim and colleagues' (2011) suggestion because even when scenes were subsequently forgotten, the hippocampus was associated with successful scene discrimination judgements.

1.3.2.4. Stimulus representations and mnemonic processing

It is important to note that a representational account of the MTL does not suggest that the MTL regions do not play a role in mnemonic processing. Rather, it suggests that while the MTL structures are critical for memory processing, their involvement is dependent on the type of stimuli involved (Graham et al., 2010; Saksida & Bussey, 2010). For example, a representational account would argue that the hippocampus would be involved in mnemonic processes (LTM, STM, declarative, or non-declarative) that involve complex spatial representations, whilst the PRC is important for memory processes for complex objects and faces. Although this prediction remains to be tested fully, there are findings from the literature that provide some support. fMRI investigations of neurologically intact individuals during maze and spatial navigation tasks, which require complex spatial processing, are consistently associated with hippocampal activity (e.g. Bohbot, Iaria, & Petrides, 2004; Doeller, King, & Burgess, 2008; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; Maguire et al., 1998; Maguire, Frackowiak, & Frith, 1997). Moreover, those with hippocampal damage have a diminished ability to perform tasks of spatial navigation (Bohbot et al., 2004; Feigenbaum & Morris, 2004; Maguire, Nannery, & Spiers, 2006; Spiers et al., 2001). Findings in amnesic patients with hippocampal lesions and fMRI neuroimaging in neurologically healthy individuals have also emphasised the importance of the hippocampus in recognition memory tasks when the stimuli consists of spatial information, like landmarks or spatial locations/context or real world scenes (Bird & Burgess, 2008a; Bird, Shallice, & Cipolotti, 2007; Bird, Vargha-Khadem, & Burgess, 2008; Cipolotti et al., 2006; King, Trinkler, Hartley, Vargha-Khadem, & Burgess, 2004; Ross & Slotnick, 2008; Taylor, Henson, & Graham, 2007). For example, two ROC recognition memory tests consisting of scenes and

unfamiliar faces were conducted on patient Jon, the famous developmental amnesic who has bilateral hippocampal damage, and aged matched controls (Bird et al., 2008). Results showed that, although his ROC curves were inconsistent with the DPSD and UVSD models of recognition memory, he had severe deficits on the scene recognition task but intact face ROC test performance. The authors suggested therefore, that the hippocampus may play a vital role in processing spatial memories in comparison to face memories (Bird et al., 2008). Similarly, studies of amnesic lesion patients and fMRI neuroimaging of health individuals have also demonstrated that the PRC is specifically involved in recognition memory for object stimuli, but not scenes (e.g. Awipi & Davachi, 2008; Cipolotti & Maguire, 2003; Staresina & Davachi, 2008; Staresina, Duncan, & Davachi, 2011; Taylor et al., 2007; Watson, Wilding, & Graham, 2012). Taken together, these studies support the notion that the PRC and the hippocampus make important contributions to object and scene memory processes respectively.

The representational account described above overlaps somewhat with the BIC model (Diana et al., 2007). For example, both accounts suggest the PRC is specifically involved in processing single items, such as objects, whilst the hippocampus creates the item-context associations vital for scene processing. There are, however, a number of differences between these two theories. Firstly, the representational view, in contrast to the BIC model has so far made no specific predictions with regards to the role of the parahippocampal cortex (Graham et al., 2010). On the other hand, the BIC model does not explicitly address the PRC and hippocampus role in non-mnemonic or non-declarative processes and considers contexts as encoded by the parahippocampal cortex in a more general manner (i.e. beyond space; Diana et al., 2007; Ranganath, 2010).

1.4. Brain connections

As the preceding overview of the literature suggests, there is a huge amount of research into the role of the grey matter structures of the MTL and their functional role in LTM, WM and higher-order perception. Relatively few studies, however, (particularly those involving human

participants) have investigated the anatomical connections of the MTL and their functional contribution to recognition memory.

1.4.1. Lesion studies of the fornix

Since the fornix is comprised predominantly of hippocampal projections, the integrity of this tract may be critical for hippocampal-dependent processes. One way of investigating the functions of the hippocampus, therefore, is to explore the functional contributions of this fiber tract.

A large number of investigations have explored the cognitive consequences of fornix transection in monkeys and rodents. In brief, early fornix disconnection studies in both rats and monkeys produced impaired ability on a variety of spatial tasks, for example, left/right discrimination learning or maze learning (D. Gaffan, 1972; D. Gaffan & Harrison, 1984; Mahut, 1971, 1972; Murray, Davidson, Gaffan, Olton, & Suomi, 1989; Walker & Olton, 1979). Moreover, tasks that require animals to remember the spatial arrangement of whole scenes are also impacted negatively by fornix damage (D. Gaffan, 1972; D. Gaffan & Harrison, 1989a, 1989b).

It is interesting to note, however, that fornix transection only leads to impairments on learning object-reward associations when they are presented in conjunction with contextual information (i.e. background scenes/items) and not when they are presented in isolation (D. Gaffan & Harrison, 1984, 1989a; Markowska, Olton, Murray, & Gaffan, 1989; Murray et al., 1989). This led Gaffan and Harrison (1989a) to suggest that fornix lesions disrupt the ability of monkeys to remember a snap shot of a scene, which would support memories that involve identifying a stimulus and its arrangement in a complex scene.

As human fornix transection is very rare there are only a handful of studies that have investigated the effect of fornix damage on declarative LTM/recognition memory in humans. In humans the fornix is most commonly transected or damaged following surgical removal of a colloid cyst (CC) on the third ventricle. This procedure, carried out because of the immediately life-threatening nature of the CC, can lead to the sacrifice of the fornix uni- or bilaterally due to

the close proximity of this tract to the cyst (see Figure 1-10 for illustration). In two very early single-case reports of intentional surgical transection of the bilateral fornix, it was reported that both patients suffered from severe memory impairments (Christiansen, 1971; Sweet, Talland, & Ervin, 1959). Impaired memory has also been associated with unilateral damage to the fornix, for example, in a single case study by Cameron and Archibald (1981) severe impairment in learning and retaining verbal information was observed after transection of the left fornix. In addition to this, a review of the application of surgical approaches to 3rd ventricle tumours in 100 cases revealed that 2 individuals whose right fornix was sectioned to achieve better exposure to the foramen of Monro had significant post-operative memory loss (Carmel, 1985). Importantly, though, CC removal alone without damage to the fornix was reported not to result in LTM impairment (Carmel, 1985; Nitta & Symon, 1985).

Despite the aforementioned CC findings, there has been some doubt as to whether fornix damage leads to memory disorder. The most notable evidence against the suggestion that bilateral fornix damage causes LTM impairment came from a large review by Garcia-Bengochea and Friedman (1987). They tabulated 142 cases of bilateral fornix damage as a result of surgical resection of the fornix to control for intractable mesial temporal lobe epilepsy and found no evidence of persistent memory impairment. This conclusion has, however, been very strongly criticised by Gaffan and Gaffan (1991) who, on close examination of the original studies, found that only 38 patients from 2 studies had bilateral fornix lesions. Additional caveats with the studies reviewed by Garcia-Bengochea and Friedman (1987) were also cited, for example, autopsies revealed that, in some cases, particular surgical methods were adopted, which may not have resulted in substantial sparing of the fornix. What is more, no formal neuropsychological assessment of the patients was undertaken pre- or post-operatively and much of the evidence against a memory impairment after fornix damage was based on notes suggesting patients had no psychiatric or neurological issues after surgery (D. Gaffan & Gaffan, 1991; Garcia-Bengochea & Friedman, 1987).

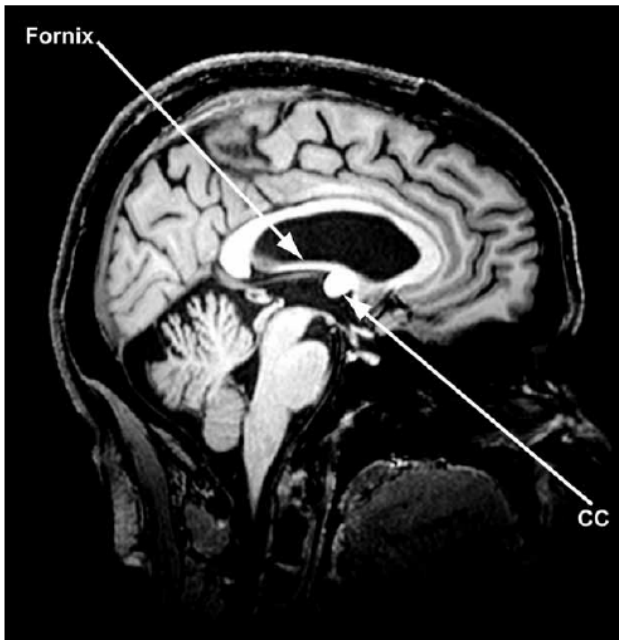

Figure 1-10: MRI scan (midline sagittal) of the third ventricle colloid cyst. The colloid cyst is immediately adjacent to the fornix. Taken from Aggleton, (2008a).

With the advent of MRI neuroimaging in the early 1990s it became possible to provide independent verification of surgical reports of fornix transection after surgery for CC or other traumatic brain injuries. A number of studies have since assessed these individuals' LTM abilities using neuropsychological and experimental tests of LTM and the results of these are summarised in Table 1-1. Gaffan et al. (1991), observed 2 fornix lesion individuals, 1 with bilateral damage and the other with unilateral left sided damage to the fornix. Both cases had exceptionally low scores on psychometric tests of verbal memory and experimental tasks of scene recognition, delayed match-to-sample and concurrent pattern and object discrimination, but relatively unimpaired non-verbal LTM abilities. Similarly, Hodges and Carpenter (1991) conducted a neuropsychological memory assessment longitudinally over 12 and 24 months of two individuals with left fornix lesions. Both individuals had exceptional impairment in verbal and non-verbal memory initially (6 months post-op) with a gradual improvement of non-verbal memory over time (12 month post-op). Profound verbal and non-verbal memory impairment was also found in an individual with bilateral resection of the fornix, following a gunshot

wound to the head although, unsurprisingly, considering the additional brain damage this patient suffered, deficits were also observed in language, WM and perception (D'Esposito, Verfaellie, Alexander, & Katz, 1995). Aggleton and colleagues (2000) assessed 12 individuals after CC surgery and found that 3 cases who had bilateral fornix damage were significantly impaired on tasks of verbal LTM and recall, but less so on tests of recognition (although recognition was impaired on the Doors and People task) in comparison to those patients without fornix damage. Finally, in a recent investigation of a bilateral fornix patient, Poreh et al. (2006) reported impairment in anterograde and, rather interestingly, retrograde memory.

As complete fornix transection and resultant amnesia are rare, recent investigations have explored the possibility of a correlational relationship between fornix damage after CC removal and LTM impairment. This methodological approach is beneficial as it allows groups of patients to be investigated and ensures that findings are not based on small numbers of individuals. In the first study to use this method, 6 CC patients had their LTM abilities measured through standard psychometric assessment and damage to their fornices was quantified through structural MRI visual ratings. Results showed that the severity of damage to the left fornix correlated significantly with the severity of impairment in verbal LTM (McMackin, Cockburn, Anslow, & Gaffan, 1995). Tsivilis and colleagues (2008) aimed to extend these findings considerably by conducting a large scale investigation of 38 individuals who had received CC surgery. In each patient, MRI volume estimates of 13 brain structures including MTL regions and the fornix were acquired along with extensive psychometric memory testing, including the administration of tasks that provided separate measures of recall and recognition. Somewhat surprisingly no relationship between patient fornix volume and their performance on tasks of recall, recognition or any other measure of long-term declarative memory were observed. On the other hand, mammillary body volume correlated significantly with 13 out of 14 tests of LTM recall performance, but not with recognition memory performance. As MB atrophy occurs after fornix damage, the authors suggested that MB volume can be taken as an indirect measure of fornix integrity and, therefore, argued that these findings provide further

evidence for the dual-process view of the MTL, where the hippocampus and its connections are vital for recall (or recollection) but not familiarity-based recognition memory (Tsivilis et al., 2008). A follow up investigation was conducted on 2 subgroups of the patients from the aforementioned study, (i.e. those with the most and the least atrophied MB) and estimates of recollection and familiarity were investigated using the R/K procedure, an ROC recognition memory task, and structural equation modeling of recall and recognition scores from standard neuropsychological tests of memory (e.g. Weschler Memory Scale; Vann et al., 2009). Analyses revealed significant impairment in recollection but intact familiarity in the most atrophied MB group in comparison to the least atrophied MB group, providing convergent data with Tsivilis et al. (2008). In summary, considered as a whole, there is strong evidence from the study of CC patients to suggest that bilateral or unilateral damage to the fornix does cause LTM impairment, particularly in tests of recall and verbal LTM.

Table 1-1: *Neuropsychological studies that have assessed LTM in human patients with damage to the fornix following surgical extraction of a colloid cyst in the 3rd ventricle. * denotes the one case where fornix damage was caused by a gunshot wound to the head. For all other cases, fornix damage was the result of surgery to remove a colloid cyst of the 3rd ventricle. LTM test key: WMS = Weschler Memory Test, WMS-R = Weschler Memory Test-Revised; WMS-III = Weschler Memory Test (3rd edition); DP = Doors and People; PA=paired associates, PAR = paragraphs; LM = logical memory; FP = family pictures; RFR = Rey Figure delayed recall; DMTS = delayed matching-to-sample. Note all subtests of the WMS, WMS-R, WMS-III and DP were carried out unless stated.*

Study	**Year**	**Patients**	**Lesion details**	**LTM assessment**	**Finding**
Gaffan and Gaffan	1991	WR GY	WR: bilateral damage to the columns of the fornix. GY: unilateral damage to the left fornix column	*Verbal* WMS: PAR, PA;WRMT words *Nonverbal* WRMT faces; RFR *Experimental* Picture recognition; DMTS; random patterns; delayed retention test, objects.	Impairment on all verbal LTM tasks. Relatively unimpaired on nonverbal psychometric tests. Impaired on all experimental tasks.
Hodges and Carpenter	1991	Case 1 (F45) Case 2 (M33)	Unilateral damage to the left fornix column in both cases	*Verbal* WMS: PAR, PA; WRMT words *Nonverbal* WRMT faces; RFR; Spatial memory test; Corsi block span	Verbal LTM impaired in both patients. Impaired nonverbal LTM at 6 months post-op with some improvement at 12 months but not to intact levels.
D'Esposito et al.	1995	Case 1 (F32)*	Damage to the left posterior parietal cortex, bilateral fornix, hippocampal commissure, right posterior temporal lobe.	*Verbal* WRMT words; Modified CVLT; Kimura recurring words test; Modified level of processing task *Nonverbal* WMS-R: Visual PA; WRMT faces; Kimura	Impairment on all tests.

				recurring figures test	
McMackin et al.	1995	6 cases	Fornix in the right hemisphere destroyed in all cases. Left fornix intact in 1 patient; some sparing in another patient.	*Verbal memory* WMS: PAR, PA;WRMT words *Nonverbal* memory RFR; Visual reproduction; Corsi blocks; WRMT faces	Correlation between verbal memory ability and severity of damage in the left fornix.
Aggleton et al.	2000	12 cases	Bilateral fornix absent in 3 cases, bilateral thinning of fornix fibres in 1 case, shrinkage of the right fornix in 1 case.	*Psychometric* WMS-R; DP; WRMT words and faces *Experimental* DMTS; Recognition/concurrent discrimination	Bilateral fornix lesion group impaired in comparison to intact group on the: WMS-R Verbal Memory, General Memory, Delayed Recall, DP recall, DP recognition (less impaired); Recognition/concurrent discrimination.
Poreh et al.	2006	AD	Complete transection of the left column and 75% damage to the right column of the fornix	*Anterograde Memory* RFR; WMS: LM *Retrograde memory* Autobiographical Memory Interview; Famous faces and public events test	Impaired on both the anterograde and retrograde LTM tests
Tsivilis et al.	2008	38 cases	3 cases of complete lesions of the fornix. Significant reduction of fornix volume in all other patients.	*Recall* WMS-III: LM; verbal PA, FP, word list recall; DP *Recognition* WRMT words and faces; WMS-III: face recognition, delayed auditory recognition, delayed visual recognition, delayed word list recognition; DP	Significant positive relationship between patients MB volume and all recall memory scores, apart from delayed visual reproduction. No correlation between MB size and recognition scores.

Vann et al.	2009	2 groups of 9 patients (large MB and small MB)	Significant MB and fornix volume differences between two groups	*Psychometric* DP *Experimental Tasks* R/K, ROC and Structural equation modelling	Small MB group was significantly poorer at the recall subtests of the DP Small MB group significant impaired recollection but intact familiarity on the R/K and ROC recognition memory tests.

Despite a number of clear findings from CC patients, it is important to consider that, as with all studies involving participants with organic or traumatic brain damage, there are a number of methodological limitations associated with fornix damage patient studies. Firstly, all the cases described have additional damage beyond the fornix and furthermore, CCs are associated with the presence of hydrocephalus (i.e. brain swelling as a result of fluid accumulation) which can impact other brain regions (Tsivilis et al., 2008). Subsequently, it is difficult to rule out the contribution of other brain regions to the significant findings in these studies (Aggleton, 2008). Additionally, excluding the recent efforts by Tsivilis, Vann and colleagues (2008, 2009), all of the reviewed studies were based on single-case or small groups of patients. Consequently, subtle cognitive deficits that may be linked to fornix damage may go undetected. With this in mind, it is ideal, therefore, that alternative methodological approaches are used to investigate the role of the fornix in mnemonic processing. New neuroimaging techniques such as Diffusion Tensor Imaging (DTI) and Resting-state fMRI (Rs-fMRI), which explore the white matter and functional networks of the brain, have only recently made this possible in neurologically intact healthy individuals. For instance, it is possible that variations in the structural integrity of the fornix may be related to differences in mnemonic ability (see Aims section below, Chapters 2 and 3).

1.4.2. The role of brain networks in recognition memory

Although this research is still in its infancy, new and exciting investigations of the large scale functional and structural networks of the brain that encompass the MTL regions have recently been conducted. Most of these studies have focused on cognitive processes associated with the prefrontal cortex, such as working memory and attention (e.g. Burzynska et al., 2011; Greicius, Krasnow, Reiss, & Menon, 2003; Redcay, Kleiner, & Saxe, 2012; M. Takahashi et al., 2010; Zou et al., 2012), although a few have examined recognition memory (Dörfel, Werner, Schaefer, von Kummer, & Karl, 2009; Fornito, Harrison, Zalesky, & Simons, 2012; McCormick, Moscovitch, Protzner, Huber, & McAndrews, 2010; Tambini, Ketz, & Davachi, 2010).

Two such investigations carried out functional connectivity analyses on fMRI data

collected as a R/K recognition memory test was carried out in the scanner (Dörfel et al., 2009; McCormick et al., 2010). McCormick and colleagues (2010) found that a small area in the left hippocampus was active during recollection in comparison to familiarity judgements. Furthermore, structural equation modelling revealed effective connectivity between the hippocampus and the inferior parietal cortex during encoding and retrieval. Interestingly the directionality of this interaction reversed during encoding and retrieval, for example, there was a positive influence from the hippocampus to parietal cortex during encoding and vice versa during retrieval (McCormick et al., 2010). On the other hand, Dörfel et al. (2009) identified a region in the left precuneus that was associated with both recollection and familiarity responses. On using this region and an MTL ROI in a psychophysiological interaction analysis, it was found that recollection responses were associated with positive connectivity between the left and right hippocampus and left precuneus, whereas familiarity responses were not (Dörfel et al., 2009).

More recently investigations have started to identify large scale networks of the brain and a few studies have investigated their functional role in declarative/recognition processes. Tambini and colleagues (2010) used Rs-fMRI in neurologically intact individuals to investigate the functional connectivity of brain regions during a rest period (i.e. during consolidation) immediately after memory encoding and just before a memory test. During the rest periods, participants had enhanced functional connectivity between the hippocampus and lateral occipital cortex in comparison to a pre-task baseline, the magnitude of which predicted individual performance on the later associated memory task. The authors suggest that these findings support theories of memory consolidation which indicate that long-term declarative memories are formed through the transfer of information from the hippocampus to the neocortex (Tambini et al., 2010). Fornito and colleagues (2012) used functional connectivity analysis of fMRI data to characterise two large scale networks of the brain, the default mode network (DMN, which includes the MTL) and the external attentional system (EAS) in healthy participants. These networks are hypothesised to operate in competition to one another, with

DMN involved in supporting internal oriented processing, whilst the EAS is a generic external attention system. Participants carried out study and test phases of a contextual recollection task in the scanner, but only the retrieval test phases were scanned. Functional connectivity analysis showed that there was increased cooperation between the DMN and a specific component of the EAS in the right frontoparietal region during contextual recollection (Fornito et al., 2012). This study indicates, therefore, that functional interactions of brain regions change depending on cognitive context.

1.5. Aims

The functional and structural brain networks that allow communication between MTL regions and the rest of the brain, and how these interactions contribute to mnemonic processing, is a relatively understudied but important field. For instance, much of the MTL literature is based on focal lesion patient studies. It is not entirely clear, however, what knock on effects MTL damage may have to brain regions to which the MTL is connected and subsequently, whether some of the cognitive deficits observed in MTL damaged patients can be explained by disruptions to structural and/or functional connectivity. DTI is a novel neuroimaging technique that allows the white matter integrity of the fibre tracts of the brain to be explored. Using this neuroimaging technique the first aim of this thesis was to investigate the fornix and its role in the recollection and familiarity components of recognition memory in healthy individuals. In Chapter 2, I explored the relationship between fornix microstructural integrity and estimates of recollection and familiarity derived from a scene and object ROC task in neurologically intact participants. In Chapter 3, I then sought to expand upon the results of Chapter 2, by assessing the same participants on a standard neuropsychological battery of tests to derive a number of recall and recognition estimates and investigating if these too are associated with fornix integrity.

Next I aimed to investigate the consequences of focal MTL lesions and associated anterograde amnesia on the functional connectivity and white matter tracts of the brain. In

Chapter 4, I report the analysis of Rs-fMRI and DTI data collected from 2 amnesic individuals (1 patient with gross bilateral MTL lesions and 1 patient with selective bilateral hippocampal damage) and 32 aged matched controls. Finally, in an effort to elucidate the mechanism by which recognition memory and white matter integrity of the fornix may be linked, I finish by describing a behavioural study in Chapter 5 that was designed to establish a cognitive training paradigm that can lead to significant improvements in LTM processes such as recollection and familiarity. This is the initial step in a large scale investigation that will next seek to determine, via DTI scanning before and after training, if white matter changes support these improvements stimulated by training. As the methodological techniques (e.g. DTI, Rs-fMRI and cognitive training) vary significantly between chapters, a general methods chapter will not be included in the current thesis. Detailed descriptions of the methods used in each experiment will, however, be presented within each chapter.

Chapter 2 - A DTI study investigating the role of the fornix FA in scene and object recognition memory

2.1. Introduction

As discussed in the previous chapter, one means of examining hippocampal involvement in recognition memory is by investigating the role of the fornix in recognition processes. Although there have been a handful of patient studies that have adopted this approach they are affected by a number of methodological issues. For example, fornix damage is often accompanied by atrophy to surrounding structures and cases of complete fornix transaction are rare. Moreover, quantifying the atrophy of human fornix damage based on structural MRI scans can be very challenging. For example, Tsivilis et al. (2008) failed to find a relationship between fornix atrophy and psychometric scores of memory despite a large sample size (n = 38) and they suggest that this was due to problems measuring the tract because of distortion and its small size (Denby et al., 2009; Tsivilis et al., 2008). This has led to suggestions that it may be almost impossible to isolate the role of the fornix in memory (Aggleton, 2008).

Diffusion tensor imaging (DTI) is a noninvasive neuroimaging technique that reveals the integrity of the white matter and the axonal organization of the brain by monitoring the diffusion process of water molecules in vivo (Le Bihan & Breton, 1985). Diffusion is the random motion of molecules resulting from their own thermal energy and occurs in three dimensions, x, y and z. Given a certain amount of time, diffusion can either be isotropic (i.e. the same in all directions) or anisotropic (i.e. longer in some direction; Figure 2-1). DTI measures the diffusion of water molecules in brain tissues where the directionality of diffusion is related to the

geometrical arrangements of local tissue micro-architecture (Le Bihan, 1995). The white matter tracts of the brain comprise of bundles of myelinated axons each surrounded by myelin sheaths. Due to this specific physiological arrangement, water molecule motion is much faster along the axon than perpendicular to it (i.e. it is anisotropic) (Basser, Mattiello, & Le Bihan, 1994).

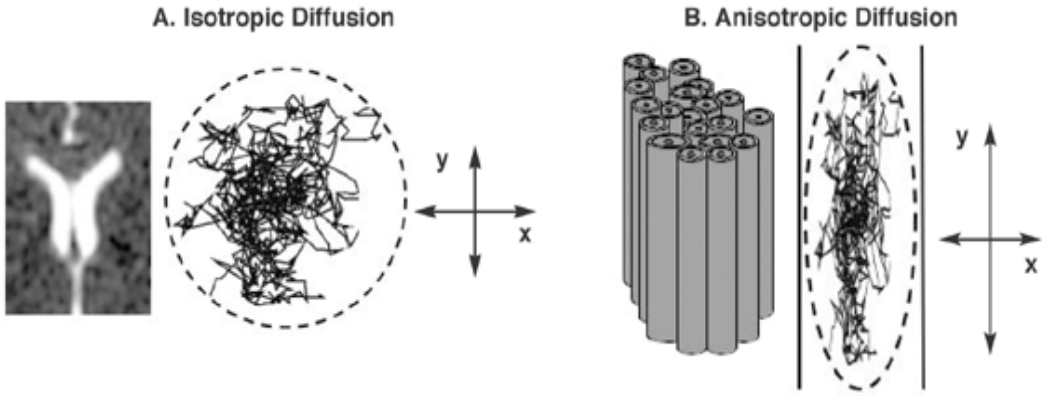

Figure 2-1: Representations of isotropic and anisotropic diffusion. (A) Isotropic diffusion – motion of molecules occurs randomly and equally in all directions when it is unimpeded, like in the ventricles of the brain, (B) Anisotropic diffusion – molecules motion is oriented more in one direction than another like in white matter tracts. Taken from Rosenbloom et al. (2003).

The diffusion tensor measures the diffusion of water molecules using a 3D Gaussian model. This 3 x 3 symmetric matrix is made up of 3 orthogonal eigenvectors and 3 positive eigenvalues (λ_1 $\boldsymbol{\varepsilon}_1$,$\lambda_2$ $\boldsymbol{\varepsilon}_2$,$\lambda_3$ $\boldsymbol{\varepsilon}_3$). The major eigenvector of the diffusion tensor ($\boldsymbol{\varepsilon}_1$) points in the principle diffusion direction of a voxel. In anisotropic tissue, therefore, this eigenvector defines the fibre tract axis of the tissue (Basser et al., 1994). In this way, the 3 orthogonal eigenvectors act as a local fibre coordinate system, whilst the 3 eigenvalues give the diffusivity in the direction of each eigenvector (Le Bihan et al., 2001).

The information gathered from the diffusion tensor can be displayed by condensing the information contained in the eigenvalues of the diffusion tensor into a single number (a scalar) or 4 values (red, blue, green colour and brightness). Two scalar values that are commonly

calculated in in every voxel of a participant's brain are fractional anisotropy and mean diffusivity. Fractional anisotropy (FA; Basser, Mattiello, & LeBihan, 1994) is the most common DTI measure and, as its name would suggest, it is the measure of the fraction of the diffusion that is anisotropic in a given voxel. In this way, FA represents the difference of the diffusion tensor ellipsoid shape from a perfect sphere. All tensor anisotropy values are normalised from 0-1 and hence, FA values approaching 1 reflect diffusion predominantly along one axis and values approaching 0 indicate diffusion in all directions, with any FA values greater than 0.2 reflecting WM tracts (Le Bihan et al., 2001). FA is thought to represent structural properties such as axonal diameter, density and myelination (Beaulieu, 2002) and is taken to reflect white matter microstructure integrity. Mean diffusivity (MD) is the average of the tensor eigenvalues and represents the average molecular motion independent of tissue directionality and is affected by obstacles, cellular size and integrity (Basser et al., 1994). MD is commonly used in DTI investigations of patient populations with white matter damage or in aging (e.g. Cercignani, Inglese, Pagani, Comi, & Filippi, 2001; Jeon et al., 2012). Finally, the main direction of diffusivities (i.e. the main ellipsoid axes), can be taken as a measure of the orientation in space of the structures (Le Bihan, 2003).

Recently, a number of investigations have suggested that variation in white matter tract integrity may have behavioural relevance (Johansen-Berg, 2010). For example, evidence indicates that the FA of pathways thought to be involved in cognitive and emotional functions correlates significantly with behavioural scores of said function (Della-Maggiore, Scholz, Johansen-Berg, & Paus, 2009; Flöel, de Vries, Scholz, Breitenstein, & Johansen-Berg, 2009; Fuentemilla et al., 2009; M. J. Kim & Whalen, 2009). Flöel and colleagues (2009), for example, found that inter-individual variability in grammar learning correlated with the integrity of fibres arising from the left, but not right, Broca's area.

A novel and alternative method to investigate the role of the fornix in recognition, therefore, would be to use DTI to assess whether microstructural variations, as measured by FA, of this tract in healthy individuals are related to differences in estimates of recollection

and/or familiarity. A previous preliminary investigation by Nestor and colleagues (2007) found that greater fornix FA in 11 neurologically healthy participants was associated with higher recall but not recognition scores on the Doors and People test (Baddeley et al., 2006), supporting the idea that the hippocampus-diencephalic pathway is important for recollective but not familiarity-based memory. Notably, however, the small number of participants led the authors to express caution in the interpretation of this finding. Moreover, one limitation of this study is that the Doors and People does not provide separate estimates of recollection and familiarity. Receiver operating characteristic (ROC), recognition memory tasks, as already discussed in Chapter 1, are one of the most valid and utilised approaches used to measure recollection and familiarity. In this task participants are asked during the test phase of a recognition memory test to respond using a 6 point confidence scale ("1" = confident an item is new; "6" = confident an item is old). Importantly, the 1-6 response scale allows ROC curves to be plotted for each participant (P(hits) vs. P(false alarms) for each consecutive confidence level). Analysis of the ROC curve then provides performance estimates for both the dual-process signal detection (DPSD; i.e. recollection and familiarity) and unequal variance signal detection (UVSD; z-slope and sensitivity) models per participant. The UVSD measures of sensitivity and z-ROC slope reflect overall accuracy and the variance of the encoded and foil items respectively. In this investigation we used DTI to derive a measure (FA) of the microstructural integrity of 25 healthy individuals' fornices. To determine whether microstructure is related to specific mnemonic processes, the relationship between FA and performance on a scene and object recognition memory tasks and two non-mnemonic control tasks was investigated (see section 2.2.1). The unitary model predicts improved fornix microstructure may be associated with better recollection and familiarity, whilst a dual-process view suggests that improved fornix microstructure may be correlated with better recollection only. If results are in line with the stimulus processing view, however, fornix FA may correlate with scene, but not object, memory irrespective of recollection and familiarity processes.

2.2. Methods

2.2.1. Participants

25 right-handed neurologically healthy volunteers (14 male; aged 22-31 years; mean = 25.30; stdev = 2.89) participated after giving written informed consent. This work received approval from the Oxfordshire Research Ethics Committee (07/H0604/115).

2.2.2. Behavioural paradigms

All behavioural tasks were programmed using Presentation software (Neurobehavioural Systems, Inc) and administered in a counterbalanced order across participants on a 15" laptop computer with 1024 x 768 pixel screen resolution.

2.2.2.1. Recognition memory tasks

One scene and one object recognition task were used. The former involved 240 grayscale photographs of unfamiliar indoor and outdoor scenes, which did not contain people, objects, or words. For the object test, 240 grayscale photos of everyday objects were used. In both tests the stimuli were split into 120 items for an encoding phase and 120 foil items, which were presented with the encoding items for a test phase. In the encoding phase participants were presented with individual images and asked whether each scene was indoor or outdoor, or each object could fit in a shoebox. Following a twenty minute delay, during which an unrelated distracter task was completed, the test phase took place. Participants were presented with the encoding items intermixed randomly with the foils and asked to make a recognition judgment for each item using a 6-point confidence scale ("1" = confident an item is new; "6" = confident an item is old).

Receiver operating characteristic (ROC) curves for each task were derived by plotting P(hits) vs. P(false alarms) for each consecutive confidence response level. Two separate models, the dual process signal detection model (DPSD; Yonelinas, 1994) and unequal variance signal detection model (UVSD; Wixted, 2007) were fit to this data. The former assumes that

recognition memory consists of independent recollection and familiarity components, whereas the latter argues that the degree of memory strength underlies recognition performance. For the DPSD model, a Microsoft Excel Solver that implements a sum of squares search algorithm was used to obtain estimates of recollection (ro) and familiarity (d') for each participant. For the UVSD model, performance was measured by two parameters: the slope of the z-transformed ROC data, which reflects the ratio of variance of the encoded and foil item noise distributions, and sensitivity (Da; calculated from the slope of the z-transformed ROC data and its y-axis intercept), which reflects overall accuracy (Macmillan & Creelman, 2005).

2.2.2.2. Control tasks

One colour discrimination and one attention task were administered. The former was a colour oddity task (Barense et al., 2007) in which four coloured squares (425 x 275 pixels) were shown in each trial (64 total), with three being an identical colour and one a different colour. Participants selected the odd-one-out by pressing the corresponding key on a keyboard, with accuracy recorded. Luminance was equal across all four squares and each colour was trial-unique.

The attention task was a motor version of the Posner cueing paradigm (Rushworth, Ellison, & Walsh, 2001). On each trial, a diamond shaped cue was followed by a coloured Gabor patch (target), both centrally presented. Participants were asked to respond to the target depending on the combination of colour and orientation (counterbalanced) of the Gabor (left-hand button-press for red/vertical and green/horizontal, right-hand button-press for green/vertical and red/horizontal). This orthogonal manipulation of the target was used so that neither feature alone specified the correct response. A lightened side of the diamond cues informed participants about the type of target that would appear, and thus the required response. Cues were valid in 54%, invalid in 18% and neutral in 28% of trials, with performance measured by correct response times.

2.2.3. Imaging data acquisition, preprocessing and analyses

For each participant, two DTI datasets and one T1-weighted anatomical scan were acquired on a 3T Trio Sonata (Siemens, Erlangen, Germany) with a 12-channel head coil at the University of Oxford Centre for Clinical Magnetic Resonance Research. For each DTI dataset, 60 volumes were acquired, with diffusion weighting isotropically measured along 60 directions using a b-value of 1000 s/mm^2 (65 slices; voxel size 2.0 x 2.0 x 2.0mm; repetition time [TR] = 9.3s; echo time [TE] = 94 ms). Six volumes without diffusion weighting (b = 0 s/mm^2) were also acquired throughout the sequence. The T1-weighted imaged was acquired using a FLASH sequence (TR = 11.2 ms; TE = 4.7 ms; flip angle = 8^o, voxel size = 1.0 x 1.0 x 1.0mm).

All image preprocessing and analyses were carried out using tools from the FMRIB Software Library (www.fmrib.ox.ac.uk/fsl). Three complementary approaches, tract based spatial statistics (TBSS), multi-fibre probabilistic tractography and white matter voxel based morphemetry (VBM) were used to investigate the role of the fornix in recognition memory. TBSS and tractography with mean FA extraction are complementary DTI analysis techniques which allow the integrity (FA) of the fornix to be measured. These techniques were conducted to account for partial voluming errors (see section 2.3.2.1) and to reduce the possibility of committing a type 1 error.

2.2.4. Tract-based spatial statistics (TBSS)

TBSS allows voxel-wise statistical comparison between individual subjects' FA maps and is described fully elsewhere (S. M. Smith et al., 2006). In brief, individual FA data were first aligned into a common space using nonlinear registration (Andersson, Jenkinson, & Smith, 2007a, 2007b). Next, a mean FA image was created and thinned to create a mean FA skeleton, which represents the centres of all tracts common to the group. The FA skeleton was thresholded at 0.2. Each subject's aligned FA data was then projected onto this skeleton by searching perpendicular to the skeleton for maximal FA values (assumed to represent tract centres). To investigate the relationship between FA and performance on the behavioural tasks

the resulting data were then fit into multiple general linear models (GLM) with one or more explanatory variables (EV) and contrasts of interest were conducted:

The DPSD GLM consisted of EVs of scene recollection, object recollection, scene familiarity and object familiarity. Contrasts included: (1) recollection versus familiarity ('[scene recollection + object recollection] – [scene familiarity + object familiarity]' and '[scene familiarity + object familiarity]' – '[scene recollection + object recollection]'); (2) scene memory versus object memory ('[scene recollection + scene familiarity] – [object recollection + object familiarity]' and '[object recollection + object familiarity]' – '[scene recollection + scene familiarity]'); and (3) scene recollection versus object recollection ('scene recollection – object recollection' and 'object recollection – scene recollection'). For the UVSD GLM the EVs were scene z-ROC slope, object z-ROC slope, scene Da, and object Da. Contrasts included: (1) z-ROC slope (scene z-ROC slope + object z-ROC slope); (2) Da (scene DA + object DA); (3) scene z-ROC slope versus object z-ROC slope ('scene z-ROC slope – object z-ROC slope' and 'object z-ROC slope - scene z-ROC slope); and (4) scene Da versus object Da ('scene Da – object Da' and 'object Da - scene Da). The colour oddity GLM had a single EV of proportion correct and a single contrast of proportion correct ('colour oddity correct'). Finally, the motor attention GLM consisted of EVs of neutral RTs, valid RTs, and invalid RTs. Contrasts were conducted to compare across all three EVs (i.e. 'valid RTs – invalid RTs', 'invalid RTs – valid RTs', 'valid RTs – neutral RTs', 'neutral RTs – valid RTs'; 'invalid RTs – neutral RTs'; 'neutral RTs – invalid RTs').

Since our a priori hypotheses pertain to the fornix we restricted the statistical analyses to this structure using a mean fornix mask, which was created on a mean group FA map using anatomical guidelines (Bilir et al., 1998). A threshold of $p < 0.005$ uncorrected, cluster size ≥ 5 voxels was applied to identify fornix regions in which there was a significant relationship between FA and a behavioural measure of interest. Since there are no predictions regarding tracts beyond the fornix, a more stringent threshold of $p < 0.001$ uncorrected, cluster size ≥ 10 voxels was used to explore the rest of the brain. All coordinates are in MNI space.

When exploring relationships between behavioural performance and fibre tract integrity using TBSS, one common method is to create an ROI and then to set an a priori uncorrected statistical threshold. For example, Flöel and colleagues (2009) defined an ROI of Broca's area and then used an uncorrected statistical threshold of $p < 0.05$, whilst, Della-Maggiore et al (2009) used a whole brain analysis and then an uncorrected threshold of $p < 0.005$. This investigation also adopted an uncorrected statistical threshold to ensure that sufficient sensitivity was maintained - correlations between microstructural integrity and behaviour are known to be subtle and therefore we aimed to protect against committing a type 2 error. It is important to note, however, that we adopted an additional analysis approach of examining how mean FA across the entire fornix was related to behavioural performance (see next section). If convergent significant findings were observed across the two approaches then it is unlikely that any significant TBSS findings were simply false positives.

2.2.5. Individual subject tractography and FA extraction

An alternative approach to TBSS involved extracting the mean FA across each participant's fornix and correlating these values with the acquired behavioural measures. Multi-fibre probabilistic tractography (Behrens, Woolrich, et al., 2003) estimates a probability distribution function (pdf) at each voxel on each fibre direction. Symmetrical tractography then proceeds by drawing multiple streamline samples through these pdfs from each voxel in a specified seed mask volume to each voxel in a specified waypoint volume and vice-versa, to create an estimate of the distribution of connections. Here, we drew fornix tail, body and column masks for each subject on their individual structural MRI scans for use as seed and waypoint masks in symmetrical tractography with 5000 streamline samples. The tail mask was drawn on a single coronal slice on which both left and right tails were fully evident, the body mask was drawn on a single coronal slice at the point where the two tails first came together and the column mask was drawn on the coronal slice at which the column was most elongated. The resulting tracking of the fornix for each participant was then binarized and overlaid on individual FA maps. This image was verified to ensure that only the fornix was included and was split into

tail, body and column segments (Bilir et al., 1998). Mean FA values were extracted for each segment from individual FA maps for statistical analysis.

2.2.6. White matter voxel-based morphometry (VBM)

Since differences in FA in narrow tracts can be confounded with variations in tract morphology, white matter VBM was used to investigate whether individual differences in fornix gross morphology are related to recognition memory performance. First pioneered by Ashburner and Friston (2000), white matter VBM interrogates the relative differences in white matter density though a voxel-wise comparison between participants structural MRI scans. One major methodological advantage of VBM is that it is conducted at the whole brain level and is hence not constrained to a priori ROI's as in tractography.

VBM (Ashburner & Friston, 2000) of white matter was carried out on the T1-weighted structural images. The T1-weighted structural images first underwent brain extraction (S. M. Smith, 2002) followed by tissue type segmentation (Y. Zhang, Brady, & Smith, 2001). The resulting white-matter partial volume images were then warped to Montreal Neurological Institute 152 space using nonlinear registration. Registered images were then modulated using the warp field to correct for local expansion or contractions and then smoothed with an isotropic Gaussian kernel (FWHM 2mm). As with TBSS, data were subjected to multiple GLMs. For statistical analyses, the same GLMs that were implemented for TBSS were used, with a statistical threshold of $p < 0.005$ uncorrected, cluster size ≥ 5 voxels.

2.3. Results

2.3.1. Behavioural performance

Table 2-1 summarizes the behavioural data from all tasks. Performance between the recognition tasks was matched (hits versus misses both $t(24) \leq 0.4$, $p > 0.6$; Figure 2-2). Estimates of scene and object recollection as derived using the DPSD model correlated significantly ($r = 0.78$; $p \leq 0.0001$) as did the familiarity estimates ($r = 0.78$; $p \leq 0.0001$). There

was no significant correlation between recollection and familiarity estimates for either scene or object tasks (both r≤0.3, p > 0.1).

There was a significant correlation between scene and object Da as derived by the UVSD model (r = 0.75, p ≤ 0.0001) but not between scene and object z-ROC slope (r = 0.017, p = 0.94). There was no correlation between z-ROC slope and Da for either scenes or objects (both r < 0.3, p > 0.1).

2.3.2. Imaging Results

2.3.2.1. TBSS

Given our *a priori* hypotheses, only results pertaining to the fornix are reported below.

DPSD model

Compared to familiarity, recollection ([scene + object recollection] – [scene + object familiarity]) was associated with two significant clusters in the fornix tail (cluster 1 max t = 5.4; x = -18, y = -30, z = 5; voxels = 5; cluster 2 max t = 3.1; x = -24, y = -33, z = 5; voxels = 6) (Figure 2-3A). FA was extracted at the most significant voxel to illustrate a significant correlation between scene (r = 0.75, p ≤ 0.0001) and object (r = 0.54, p = 0.006) recollection and FA, but not between either familiarity estimate and FA (both r < 0.1, p > 0.5) (Figure 2-3B-C). These results were supported by an additional contrast which investigated the correlation between FA of the fornix and recollection alone (scene + object recollection). This contrast was associated with one cluster of correlation within the fornix (max t = 5.38; x = -18, y = -30, z = 5) which was in the same location as cluster 1 from the 'recollection-familiarity' contrast described above. For familiarity, the comparison ([scene + object familiarity] – [scene + object recollection]) revealed no significant clusters of correlation in the fornix. These findings were also supported by the familiarity alone contrast (scene familiarity + object familiarity) which also revealed no signficant clusters of correlation with the fornix FA. Taken together these findings suggest that there was no region within the fornix at which there was a significant relationship between familiarity and FA.

Table 2-1: Behavioural performance across all tasks

Task	Measure	Mean	S.D.	Range
Scene ROC	Hits	0.72	0.08	0.58–0.87
	Misses	0.28	0.08	0.13–0.42
	ro	0.37	0.16	0.10–0.72
	d’	0.65	0.40	-0.04–1.49
	z-ROC slope	0.72	0.12	0.43–0.98
	Da	1.17	0.46	0.56–2.18
Object ROC	Hits	0.73	0.10	0.35–0.90
	Misses	0.27	0.11	0.10–0.74
	ro	0.42	0.18	0.15–0.72
	d’	0.79	0.51	-0.51–1.63
	z-ROC slope	0.84	0.19	0.51–1.15
	Da	1.14	0.39	0.74–2.55
Colour Oddity	Proportion correct	0.78	0.10	0.60–0.94
Motor attention	Neutral response times/ms	8095	1255	6204–11536
	Valid response times/ms	7431	1279	5111–9720
	Invalid response times/ms	8395	1357	6173–11166

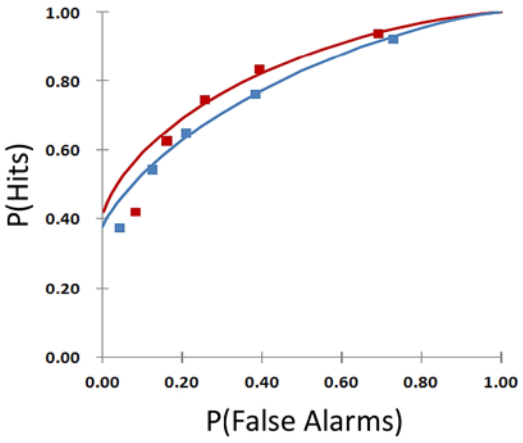

Figure 2-2: The average ROC curves for the scene (blue) and object (red) recognition tasks.

to study using TBSS since narrowness and geometry of the tract can cause relatively low FA. Consequently, when individual subject maximal FA values are projected onto the mean FA skeleton, values can be projected from nearby fibre tracts rather than the fornix itself. To assess

this in our data the significant TBSS clusters were deprojected back into each subject's native space. Although most voxels from within these clusters deprojected back into the fornix for all subjects, a small proportion of cluster voxels were found to have been erroneously projected from the internal capsule in 16 participants. To test whether our correlations still stood without the contribution made by these voxels these voxels were manually removed from individual subject FA skeletons and calculated mean FA across remaining voxels. After this editing, a significant correlation was still found between FA and scene recollection ($r = 0.51$; $p = 0.01$) and object recollection ($r = 0.43$; $p = 0.05$) but not between FA and object or scene familiarity (both $r > 0.1$, $p > 0.4$).

The possibility that scene and object memory may correlate differentially with fornix FA was also explored. The contrast '(scene recollection + familiarity) – (object recollection + familiarity)' revealed a significant cluster in the fornix tail (max $t = 3.4$; $x = -18$, $y = -31$, $z = 6$; voxels = 5). This cluster is almost identical to that observed in association with recollection as shown in Figure 2-3A, and is driven by a higher correlation between scene recollection and FA in comparison to that between object recollection and FA in this region (with no significant relationship between FA and scene or object familiarity). To confirm this, the contrast 'scene recollection – object recollection' identified the same cluster (max $t = 4.0$, $x = -18$, $y = -30$, $z = 5$; voxels = 6). No suprathreshold clusters emerged for object memory (i.e. [object recollection + familiarity] – [scene recollection + familiarity]).

UVSD model

Neither measures of performance, slope nor sensitivity parameters, were associated with any suprathreshold clusters of correlation.

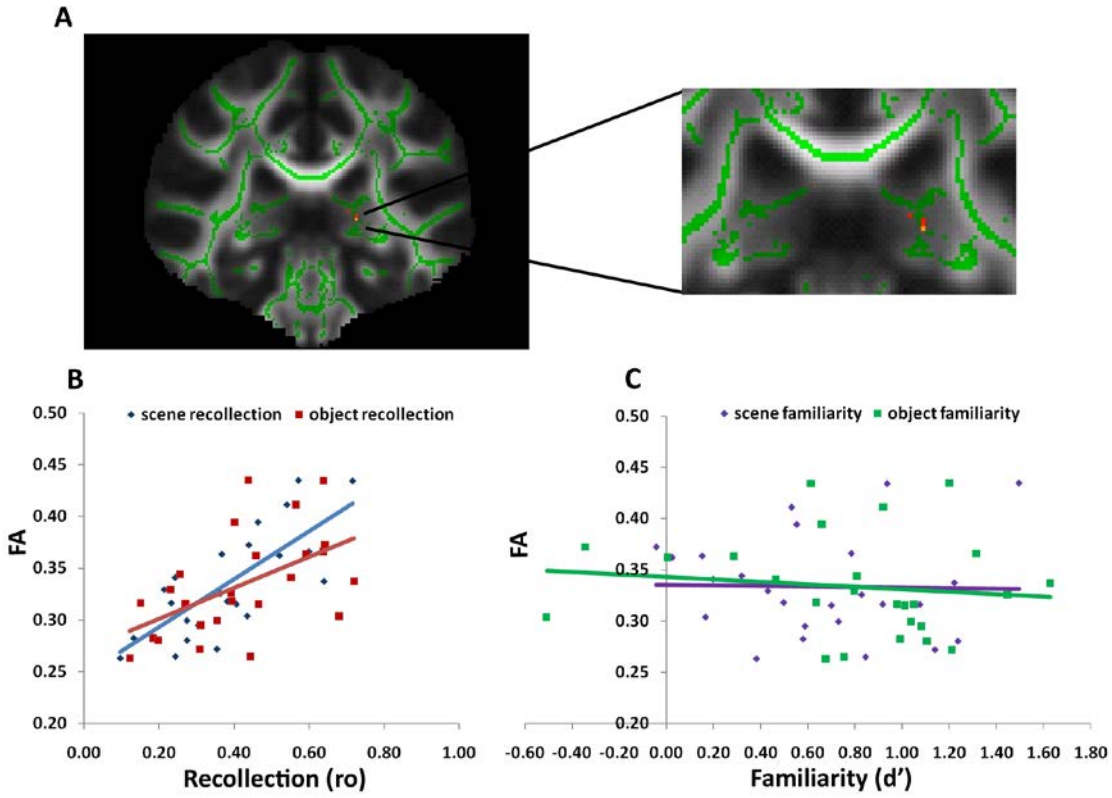

*Figure 2-3: (**A**) Positive correlation between FA and recollection in the left fornix tail as identified by TBSS (max t = 5.4). Clusters are overlaid on the mean FA image and white matter skeleton (green voxels) of all participants. At the max t-stat voxel (-18, -30, 5) there was a significant correlation between (**B**) FA and scene (r = 0.75) and object (r = 0.54) recollection but not (**C**) between FA and scene and object familiarity (both r < 0.1).*

Control tasks

No behavioural measures from either the colour oddity or attention task were associated with significant clusters of correlation, supporting the notion that the fornix is particularly important for mnemonic processing.

2.3.2.2. Individual subject tractography and FA extraction

DPSD model

Confirming the TBSS findings, mean FA of the fornix tail correlated significantly with scene

recollection (r = 0.43; p = 0.034), with a strong trend towards significance for object recollection (r = 0.38; p = 0.060). There was also a trend towards a significant correlation between fornix body mean FA and scene recollection (r = 0.37, p = 0.071) but not between fornix body and object recollection nor column mean FA and scene or object recollection (all r < 0.3, p > 0.1). There were no significant correlations between fornix tail, body, or column mean FA and either scene or object familiarity (all r < 0.3, p > 0.1).

UVSD model

Other than a trend towards significance between scene sensitivity and fornix column mean FA (r = 0.38, p = 0.062), all other UVSD estimates for the scene (all r < 0.4, p > 0.09) and object (all r < 0.3, p > 0.3) tasks did not correlate with fornix tail, body, or column mean FA.

Control tasks

No behavioural measures from either control task correlated significantly with mean FA in the fornix tail, body, or column (all r < 0.3, p > 0.1).

2.3.2.3. White matter VBM

There were no significant correlations between gross morphometry of the fornix and any of the recognition memory estimates or control task behavioural measures.

2.4. Discussion

Using DTI the involvement of the fornix in recognition memory has successfully been investigated in isolation from other structures. Individual differences in the white matter microstructure of this tract, specifically in the tail region, were found to reflect variation in recollection but not familiarity memory on two recognition tasks when behaviour was modelled by a dual-process model of recognition memory (DPSD; Yonelinas, 1994). There was no significant relationship between fornix microstructure and memory performance when behaviour was modelled by a unitary model of recognition memory (UVSD; Wixted, 2007), nor performance on two non-mnemonic tasks (colour discrimination and attention).

The current study supports the idea that there are distinct MTL-medial diencephalon pathways that mediate different memory processes (Aggleton & Brown, 1999). As the fornix is comprised predominantly of hippocampal connections, the data underlines the suggestion that the hippocampal-diencephalon pathway does not play a general role in recognition memory but is particularly important for recollection (Aggleton & Brown, 1999; Eichenbaum et al., 2007). Our findings are consistent with reports of a role for the hippocampus in recollection but not familiarity memory (Aggleton, Vann, Denby, et al., 2005; Davachi et al., 2003; Ranganath et al., 2004; Yonelinas et al., 2002) and disagree with the suggestion that memory strength is a more critical determinant of MTL involvement in recognition (Squire et al., 2007). The present data also support work that has associated fornix and medial diencephalic damage in human amnesic patients with disproportionate impairment in recollection (Tsivilis et al., 2008; Vann et al., 2009) but, importantly, adds to these studies by identifying, for the first time, the involvement of the fornix in isolation from neighbouring structures such as the mamillary bodies.

Interestingly, an effect of stimulus type was found, with a more significant relationship between fornix FA and scene recollection memory than that between fornix FA and object recollection. This is not surprising since the hippocampus is critical for spatial cognition (O'Keefe & Nadel, 1978). Indeed, recent work has suggested that stimulus type (objects/scenes) may be a more important determinant of MTL involvement than process type (recollection/familiarity) in recognition memory, with reports of impaired scene but intact face recognition memory in patients with hippocampal damage (Bird & Burgess, 2008b; Cipolotti et al., 2006; Taylor et al., 2007). At first glance, the findings do not fit entirely with this view: there was no significant relationship between scene familiarity memory and fornix FA, and better object recollection was associated with improved fornix microstructure. It is possible, however, that the results can be reconciled to a stimulus-dependent view by considering the relationship between recollection and spatial cognition. Recollection is defined by the remembering of contextual information and as such, may often be associated with greater spatial processing,

irrespective of the stimulus material presented. Likewise, a familiarity trace for a spatial scene may only require minimal spatial processing of that scene and thus, may occur independently from the hippocampus. The relationship between stimulus type and mnemonic process is undoubtedly complex (see Bird & Burgess, 2008a; Diana et al., 2007) and requires much investigation if functional specialization within the MTL is to be fully understood.

The current results support previous neuropsychological studies that reported significant correlation between fornix FA and recall performance on 2 different standard memory tasks (Doors and People Test and Free and Cued Selective Reminding Test) in 11 healthy participants and healthy aging adults (Metzler-Baddeley, Jones, Belaroussi, Aggleton, & O'Sullivan, 2011; Nestor et al., 2007). Critically, our findings build considerably upon this by identifying the specific mnemonic processes that the fornix may be important in a large group of participants.

2.4.1. Biological Interpretations

As with any correlational finding, it is difficult to discern causation from the current results. For example, it is unknown whether training in an individual's recall and recognition ability over time leads to augmented fornix microstructure, or whether individuals with innately enhanced fornix microstructure possess better recall and recognition memory. Research has just begun to disentangle the complex interaction of experience and predetermined genetic factors on white matter integrity within the brain. For example, a recent twin study revealed through structural equation modelling at each brain voxel that genetic factors explained 75 - 90% of the variance in FA especially in large fibre bundles (Chiang et al., 2009). In contrast, three longitudinal training studies have recently shown that training in reading, motor learning and working memory leads to increased FA in the white matter tracts that support these skills (Keller & Just, 2009; Scholz, Klein, Behrens, & Johansen-Berg, 2009; Takeuchi et al., 2010). Although the current study cannot shed light on the complex interaction between genetic and environmental influences on white matter, it is nevertheless important to elucidate the biological significance

of our findings. FA is believed to reflect axon density, myelination and diameter (Beaulieu, 2002). The degradation of white matter microstructure, particularly myelination, with ageing has been suggested to contribute to cognitive decline by reducing axonal conduction speeds and disrupting the function of neuronal networks (Peters, 2002). It is possible, therefore, that improved fornix microstructure in neurologically healthy individuals may lead to more efficient transfer of information between the hippocampus and medial diencephalon and subsequently, other structures involved in recollection (Fields, 2008). This, in turn, may lead to enhanced encoding and retrieval of information across neural circuits, resulting in better recollective memory.

2.4.2. Methodological Issues

Whilst DTI is currently the only neuroimaging technique that allows the in-vivo exploration of the white matter tracts of the human brain, it is still a relatively novel technique that is associated with a number of limitation (for review see, Jones & Cercignani, 2010). Firstly, in DTI, diffusion is measured averaged over a voxel which is typically a few millimetres large. An axons diameter, however, is 1-15 µm, so there is considerable mismatch between the spatial resolution of DTI and the size and scale of individual axons. This is an issue when you consider that FA, which is often interpreted (as in this study) as "white matter integrity", is affected by many varied factors, such as change in myelination, increase in intracellular or extracellular water and cell death. Due to DTI's poor spatial resolution it is, therefore, impossible to know the contributions of these factors on FA and subsequently the biological interpretation of DTI findings can be difficult to make.

Another methodological issue to consider is that due to the orientation and narrow dimensions of the fornix, the use of DTI and TBSS to study this tract can be prone to partial volume errors affecting the estimation of FA at a voxel level. When fibre tracts are crossing or fanning, the diffusion tensor cannot represent this well at the voxel level due to the spatial resolution issues described above. This is problematic as a significant numbers of white matter

tracts contain multiple fibre bundles that are orientated in different directions and in these regions it would be expected that the diffusion tensor is not reliable (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007). In tractrography, where directionality of the tensor is crucial, this can lead to false positives and negative fibre tracts. Indeed, a common false negative with DTI tractography is the lateral lip/hand connections of the corticospinal tract (Behrens et al., 2007). Additional partial volume errors can occur when 2 different types of tissue, for example, CSF and white matter tract, are present in a single voxel. This can result in a diffusion tensor that represents neither tissue well and, subsequently, may lead to further tractography false positives or negatives. To address this concern of partial volume errors, we conducted a number of complementary analyses to ensure that any significant findings were related to FA, and thus white matter microstructure, in the fornix only. First, any significant TBSS clusters at a group level were deprojected back into individual subject space so that any projection errors from neighbouring tracts could be identified and their contribution removed. Second, probabilistic tractography was used to identify each participant's fornix, from which mean FA was extracted and correlated with the acquired behavioural measures. Finally, white matter VBM was conducted to investigate whether any significant TBSS results could be accounted for, at least partially, by individual differences in gross fornix morphology. Critically, the findings from all three approaches were highly consistent. Both TBSS and the extraction of mean FA from individual fornices implicated FA in the fornix tail as being significantly related to recollection but not familiarity memory. Moreover, differences in fornix morphology were not found to be related to recollection memory performance.

Although FA in the fornix tail was strongly implicated in this study, a similar relationship was not observed between FA in the fornix body or column and recollection memory. It is unclear why this specific relationship was found. The tail section is the most narrow segment of the fornix and since FA is sensitive to fibre complexity and compression. It is therefore conceivable that FA values in the fornix tail are more likely to fluctuate to a larger degree across individuals due to the higher fibre density in this region.

Finally, the use of the ROC approach to assess recognition memory performance also needs to be considered critically. Although ROC-curves are currently the most highly utilized and reliable method for estimating recollection and familiarity, there are a number of methodological issues associated with the sum of search algorithm that was utilized in this investigation. Firstly, the Microsoft Excel Solver can have variable success in fitting an ROC curve to a participant's confidence judgements. The success of the ROC curve fit is dependent on a number of factors, some of which cannot be controlled by the investigator. For example, even if the hits and false alarm data is kept constant, the Microsoft Excel Solver will give slightly different parameter estimates of recollection and familiarity. A controllable factor is the starting parameter values entered into the Microsoft Excel Solver. In this investigation, in an effort to reduce variability between participants' ROC curves, the original parameter values inputted by Yonelinas were used for every ROC calculated (e.g. recollection = 0.27, familiarity = 0.4; Criterion = 0.5, 0, -0.5, -1, -1.5). Despite this, however, some ROC curves were not fit optimally to all data points, for example, as seen in the average scene and object ROC curve (Figure 2-2).

The fit of the ROC can be changed by adjusting the initial starting parameters. Using the average scene ROC data from Figure 2-2 two examples of the effect of changing the original parameters on the success of ROC fit are displayed in Figure 2-4. Figure 2-4(A) shows that after the initial parameter of recollection is changed to 0.4, the ROC fit improves and the recollection and familiarity parameters change slightly (recollection = 0.28; familiarity = 0.76). Figure 2-4 (B), on the other hand, indicates that altering the variable oldvar (i.e. the variance of the old item distributions) to 0.9 leads to a somewhat improved ROC fit (recollection = 0.32; familiarity = 0.68).

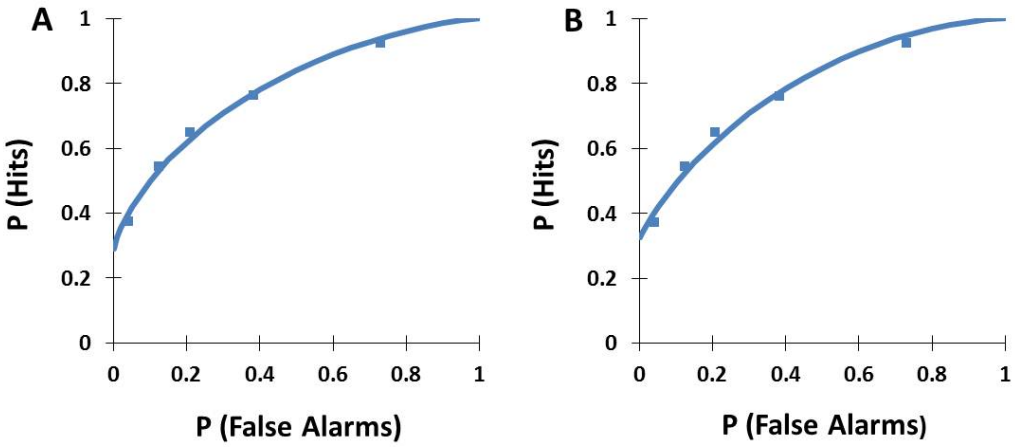

Figure 2-4: The average scene ROC when the initial recollection parameter is 0.4 (A) and when the oldvar value is 0.9 (B).

Another methodological issue with ROC curves experienced in this study is the prevalence of negative estimates of familiarity, with 2 negative object familiarity scores and 1 negative scene familiarity score observed (see Figure 2-3). The ROC analysis method for determining parameters of recognition memory is very sensitive to the equal spread of responses across all 6 confidence levels (Yonelinas & Parks, 2007). Although we instructed participants to use all confidence levels equally, it appears that, on inspection of the data, those that obtained negative familiarity scores had failed to use a particular confidence level or biased their responses to the extremes of the scale. This leads to the ROC-curve becoming skewed towards the right and left most corners. As their estimates of familiarity are unreliable there is an argument for excluding these participants from our analysis. Critically, however, TBSS was rerun doing this and this showed that including these participants did not lead to any significant changes to our findings. Bearing this and a desire to include as high a number of participants as possible in our neuroimaging analysis in mind, it was decided to include these two participants despite their somewhat biased confidence responses.

Finally, one obvious question that the current study raises is whether the findings can be extended to other measures of episodic memory, such as recall and recognition, as assessed by standard neuropsychological tests. Considering Nestor et al. (2007) and the current chapter's results, it might be predicted that FA may correlate significantly with tests of recall in

comparison to recognition. In Chapter 3, we reassessed the participants from Chapter 2 on a standard battery of EM tests to investigate this possibility.

Chapter 3 - A follow up DTI study into the role of fornix in standard scores of episodic long-term memory

3.1. Introduction

In Chapter 2 we demonstrated that the integrity (FA) of the fornix correlated with recollection but not familiarity as measured by a scene and object ROC recognition memory test. The aim of the current study was to determine whether these findings could be generalised to other tests of recognition memory, in particular standard neuropsychological tasks. To date, although various studies have investigated white matter structure in the brain and individual differences in mnemonic function (Goldstein et al., 2009; Sasson, Doniger, Pasternak, & Assaf, 2010) only a few have concentrated on the fornix. As discussed in Chapter 2, Nestor et al. (2007) found that greater fornix FA in 11 neurologically healthy participants was associated with higher recall but not recognition scores on the Doors and People test (Baddeley, 1994). In a more recent study, Metzler-Baddeley and colleagues (2011) showed by utilizing deterministic tractography to measure the FA of the fornix, UF and parahippocampal cingulum in a group of healthy older adults (53-93 years), that the FA of the fornix was associated with free recall performance from the Free and Cued Selective Reminding Test (FCSRT; Grober & Buschke, 1987), whilst UF FA decline was linked to impairment in error monitoring from a Paired association learning test (PAL). However, no other raw subtest measures from the psychometric memory tests used in this investigation including the Doors and People (Baddeley et al., 2006), FCSRT (Grober & Buschke, 1987) or the PAL test, were associated FA in these tracts (Metzler-Baddeley et al., 2011).

The present study sought to expand upon the findings of Nestor et al. (2007) and Metzler-Baddeley et al. (2011) by using a battery of standard neuropsychological memory tests to determine if there is a relationship between task performance and FA of the fornix. We reassessed the same participants from Chapter 2 using the Doors and People (Baddeley et al., 2006), the Recognition Memory Test (RMT) for faces and words (Warrington, 1984) and the Logical Memory and Family Pictures subtests from the Wechsler Memory Scale 3rd edition (WMS-III; Wechsler, 1999). These tests gave rise to 8 recall and 3 recognition estimates per participant. Psychometric tests measuring recall are expected to be based on the recollection processes alone, whilst tests of recognition are based on both recollection and familiarity.

If our findings are in line with Chapter 2 and previous research (Metzler-Baddeley et al., 2011; Nestor et al., 2007) it might be expected that higher performance on a battery of recall neuropsychological memory tests will be related to improved fornix microstructure. This would also further support the dual-process view of the functional contribution of the MTL to long-term declarative memory. On the other hand, if our results are consistent with the unitary model, improved fornix microstructure may be associated with increased performance on tasks of both recall (recollection) and recognition (recollection and familiarity).

3.2. Methods

3.2.1. Participants

The same 25 participants as Chapter 2 took part in the current investigation (see section 2.2.1 for full details).

3.2.2. Behavioural paradigms

3.2.2.1. Neuropsychological Tests

The following tests were administered in accord to their respective published instructions. Resulting scaled scores of these tests were computed according to the test norms:

(1) All subtests of the Doors and People (Baddeley et al., 2006). Participants were assessed on their ability to recognize doors and names of fictitious people, and learn and recall the names of people and abstract shapes. For both the recognition and recall tasks there were immediate and delayed (30min) conditions.

(2) RMT (Warrington, 1984) for 50 faces and 50 words. In these tasks, participants were shown a series of photographs of faces or words separately and were then immediately administered a forced-choice recognition memory task for each stimuli type. The word test results were excluded from this study because performance was at ceiling.

(3) The Logical Memory and Family Pictures subtests from the WMS-III (Wechsler, 1999). Participants were tested on their ability to recall two stories read aloud to them by the experimenter (Logical Memory) and specific details of four family scenes they had previously studied (Family Pictures) in both immediate and delayed (30min) recall conditions. In the delayed condition an unrelated motor attention distractor task was administered between the encoding and retrieval sessions.

Two composite scores of average recognition and average recall ability were calculated from these neuropsychological tests. The recognition index was the average scaled score of the three recognition memory tests from the faces Recognition Memory Test and the Doors and People test, whilst the recall score was the mean scaled score of the eight recall memory tests from the WMS-III and the Doors and People test.

3.2.3. Tract-based spatial statistics (TBSS)

Considering our *a priori* hypotheses TBSS was carried out on a mean fornix mask as described in Chapter 2 section 2.2.5. To investigate the relationship between FA and performance on the behavioural tasks the resulting data were then fit into multiple general linear models (GLM) with one or more explanatory variables (EV) and contrasts of interest were conducted.

The performance on WMS-III Logical memory and Family Pictures were fit into separate GLM's, all with EVs of immediate recall and delayed recall. Contrasts for these tests included (1)

immediate recall ('immediate recall'), (2) delayed recall ('delayed recall') and (3) overall recall ('immediate recall + delayed recall'). RMT face recognition GLM consisted of a single EV of recognition performance and a single contrast of recognition performance ('recognition performance'). The Doors and People GLM consisted of EV's of recall and recognition with contrasts of (1) recall ('recall-recognition'), (2) recognition ('recognition-recall') and (3) overall performance ('recall' + 'recognition'). The composite GLM consisted of EVs of average recognition and average recall with contrasts of recognition versus recall ('average recognition - average recall' and recall versus recognition 'average recall - average recognition').

Again a threshold of $p < 0.005$ uncorrected, cluster size ≥ 5 voxels was applied to identify fornix regions in which there was a significant relationship between FA and a behavioural measure of interest. All coordinates are in MNI space.

3.2.4. Individual subject tractography and FA extraction

The same mean FA values of the participant's fornix tail, body and column were used in this study as those computed in Chapter 2 (see section 2.2.5 for methodological details). These were correlated with the participant's standard scores of episodic memory.

3.2.5. White matter voxel-based morphometry (VBM)

VBM was conducted following the procedure described in section 2.2.6 and subjected to multiple GLMs. For statistical analyses, the same GLMs that were implemented for TBSS were used, with a statistical threshold of $p < 0.005$ uncorrected, cluster size ≥ 5 voxels.

3.3. Results

3.3.1. Behavioural Performance

Table 3-1 summarizes the behavioural data for all memory tests. For the standard memory tests, Doors and People recognition correlated significantly with the WMS-III Logical memory delayed recall scores (all $r > 0.47$, $p < 0.02$). WMS-III Family pictures immediate and delayed recall correlated significantly with one another ($r = 0.949$, $p \leq 0.0001$), as did the WMS-III

Logical memory immediate and delayed recall ($r = 0.79$, $p \leq 0.0001$). No other neuropsychological tests scores correlated to a significant level (all $r > -0.26$, $p > 0.19$).

Table 3-1: Behavioural performance across all tasks.

Task	Measure	Mean	S.D.	Range
WMS-III Logical memory	Immediate recall	11.8	2.33	8-17
	Delayed recall	12.08	2.17	8-17
WMS-III Family Pictures	Immediate recall	8.84	2.98	3-14
	Delayed recall	8.88	3.22	2-14
RMT	Face recognition	8.2	2.72	4-15
Doors and People	Recall	12.4	2.1	8-15
	Recognition	11.92	3.03	5-16

3.3.2. Track Based Spatial Statistics (TBSS)

Given our *a priori* hypotheses, only results pertaining to the fornix are reported. TBSS revealed that a proportion of the neuropsychological memory test scores correlated significantly with fornix FA, even after corrections were made for projection errors. These included the Doors and People recall, Recognition Memory Test for faces, WMS-III Logical memory delayed recall and the WMS-III Family Pictures immediate recall (Table 3-2). To visualize these relationships further individual participant FA was extracted at the most significant voxel for each memory test and plotted against that memory test performance (Figure 3-2). All other contrasts involving individual test scores as well as composite scores did not identify any clusters of correlation.

Table 3-2: Significant clusters of correlation between standard memory test scores and fornix FA as revealed by TBSS (coordinates of max t-stat in MNI space, x, y, z).

Significant cluster		Recognition memory test faces*	WMS-III Logical memory delayed recall*	WMS-III Family Pictures immediate recall	Doors and People recall - recognition
1	Max t	4.16	4.23	3.07	3.48
	Coordinates	-4, -23, 17	5, -24, 17	4,-18,18	18,-31,10
	Cluster size	56	55	5	7
2	Max t	3.69	3.03		
	Coordinates	-24, -34, 6	-5, -19, 15		
	Cluster size	15	6		
3	Max t	3.29			
	Coordinates	4,-19, 18			
	Cluster size	6			
4	Max t	3.26			
	Coordinates	-14, -32, 10			
	Cluster size	6			
5	Max t	3.66			
	Coordinates	23, -33, 5			
	Cluster size	5			

* denotes that a significant tractography result was also found.

3.3.3. Individual subject tractography and FA extraction

Considering the partial voluming errors associated with TBSS found in Chapter 2, the same alternative approach of extracting the mean FA across each participant's fornix using multi-fiber probabilistic tractography was employed (Behrens, Johansen-Berg, et al., 2003). RMT face recognition and WMS-III Logical Memory delayed recall both significantly correlated with the FA of the tail of the fornix (all $r > 0.49$; $p < 0.01$) but not the body or the column (all $r < 0.35$; $p > 0.07$). Neither the Doors and People recall nor the WMS-III Family Pictures immediate memory performance correlated with the FA of the tail, body or column of the fornix (all $r < 1$; $p > 0.5$). Unexpectedly, the WMS-III Logical Memory immediate correlated with the FA of the fornix ($r = 0.44$; $p = 0.03$). There were no significant correlations between fornix tail, body, or column mean FA and any other neuropsychological memory scores (all $r < 0.26$, $p > 0.11$).

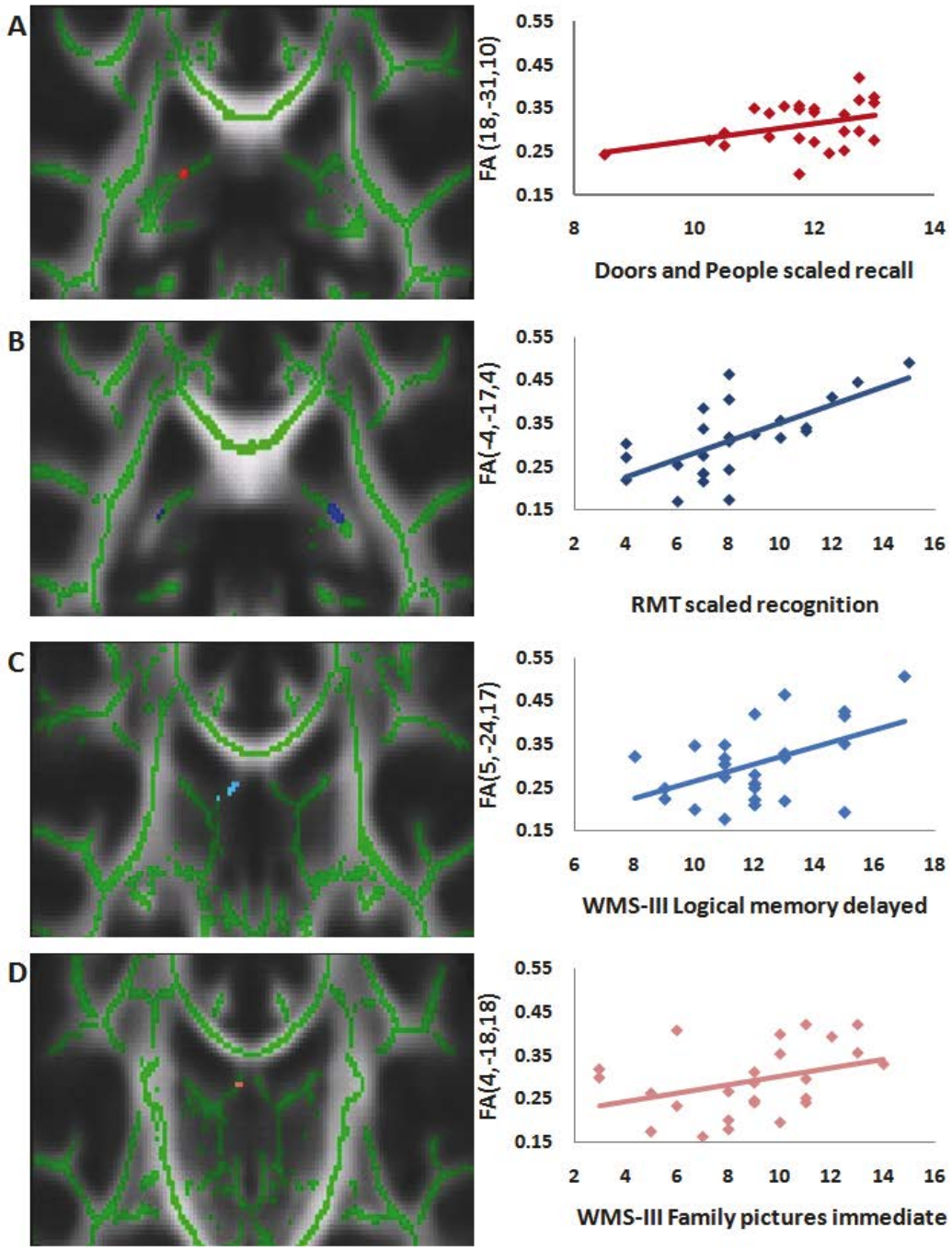

Figure 3-1: Visualization of the positive clusters of correlation between FA and memory performance as identified by TBSS. Individual participant FA at the most significant voxel for each memory test is plotted against the memory test performance; ***A*** *= DP recall (r = 0.38; p = 0.06),* ***B*** *= Recognition Memory Test for faces (r = 0.66; p ≤ 0.0001),* ***C*** *= WMS-III Logical Memory delayed (r = 0.47; p = 0.017) and* ***D*** *= WMS-III Family Pictures immediate (r = 0.37; p = 0.069). For display purposes, the statistical images were thresholded at p = 0.01 (uncorrected) and overlaid on the* MNI template and white matter skeleton (green voxels) of all participants.

3.3.4. White Matter VBM

White matter VBM analyses revealed no significant correlation between gross morphometry of the fornix and any scores of long-term episodic memory.

3.4. Discussion

The advent of DTI has provided a means by which the relationship between the microstructure of white matter neural tracts and cognitive function can be investigated. In Chapter 2 we used this technique to examine the role of the fornix in recognition memory, with higher FA in this tract in neurologically healthy young participants being associated with greater recollection but not familiarity memory performance on two ROC recognition memory tasks. Here, we investigated whether this finding could be extended to a wider range of memory tasks, using a standard battery of neuropsychological memory tests. As expected, TBSS revealed that scores on a number of tests correlated significantly with fornix FA, with the pattern of findings from the Doors and People task supporting our previous work (Nestor et al., 2007). It is clear, however, that a correlation between fornix FA and mnemonic performance was not seen across all tests, raising questions over the use of standard memory tests together with DTI in the investigation of fornix function in young healthy participants.

The results in Chapter 2, demonstrating a positive correlation between fornix white matter microstructure integrity and recollection memory, supports the idea that there are distinct MTL-diencephalic systems, with the hippocampal-diencephalic pathway being critical for recollection memory (Aggleton & Brown, 1999). Since episodic recall is thought to rely on recollection whereas recognition memory can be construed of recollection and/or familiarity memory we expected that while both recall and recognition memory performance on the standard memory tests used could correlate with fornix FA, the former should correlate with fornix FA to a greater extent than the latter.

Consistent with the idea that the fornix mediates recollective memory and that recollection contributes to both recall and recognition memory, our TBSS analyses indicated

that superior performance on a number of the standard neuropsychological tests was associated with higher FA in the tail region of the fornix in both hemispheres, including Doors and People recall in comparison to recognition performance, WMS-III Logical Memory delayed recall, WMS-III Family Pictures immediate recall, and also, the Recognition Memory Test faces. These findings, in particular those from the Doors and People test, support Chapter 2 findings and extend previous work by Nestor and colleagues (2007), who found in a smaller group of neurologically healthy participants (n = 11) that fornix FA correlates significantly with Doors and People recall but not recognition.

It is important to acknowledge, however, that a significant relationship between fornix FA and memory performance was not identified using TBSS across all tasks, with no significant clusters of correlation between fornix FA and performance on the immediate recall condition of the WMS-III Logical Memory task, and the delayed recall condition of the WMS-III Family Pictures. A lack of consistency in the findings across all tests is reflected in the fact that TBSS revealed that neither the recall nor recognition composite scores were associated with significant variations in fornix FA. This is surprising since if variations in fornix white matter microstructure are thought to be associated with differences in recollective memory ability, then one would expect this relationship to be evident across all, rather than a proportion, of the standard memory tasks that were used here. What is more, the most significant cluster of correlation observed in this investigation was between the RMT for faces and fornix FA, with both TBSS and tractography results indicating a strong positive relationship between the two. The RMT for faces is a standard test of face recognition, and performance on this test may be mediated by recollection and/or familiarity. Although we cannot ascertain which recognition memory process was utilised by the neurologically intact participants during this test in the current study, one may speculate on the basis of the findings in the previous chapter (i.e. fornix FA correlated with recollection but not familiarity) that they may have predominantly used a recollective process to make their Old/New decisions on the RMT, thus leading to a significant relationship between fornix FA and RMT performance. Further behavioural measures would be

necessary to validate this suggestion empirically, for example, by instructing subjects to give a 'remember' (recollection) or 'know' (familiar) response to each item classified as 'old'.

Notably, further inconsistencies were observed between the TBSS and tractography findings. For example, only the RMT faces and Logical Memory delayed recall TBSS clusters were backed up by correlations between mean FA of the fornix and the EM scores. Doors and People recall and Family Pictures immediate TBSS clusters were not supported by their tractography result, although these clusters did remain after editing was carried out to correct for partial voluming. These inconsistencies render it difficult to make any strong conclusions on the basis of the current data.

3.4.1. Methodological Issues

One possible interpretation for the lack of consistency in findings across the standard memory tasks is that these tests may, in general, lack the necessary sensitivity to characterize the differences in recollective memory ability that may be associated with variations in fornix white matter microstructure. Unlike ROC recognition memory tests, these psychometric tasks do not provide separate quantitative measures of recollection and familiarity, with recall scores assumed to reflect recollection, and recognition performance believed to reflect both recollection and familiarity. Additionally, it is possible that these tests, designed to be sensitive to the presence of brain damage and ageing, are less effective at detecting variation in young neurologically intact individuals. It is important to note that other DTI investigations of neurologically intact participants have found significant results using the same standard measures for which we observed no significant findings (Charlton, Barrick, Markus, & Morris, 2009; Nestor et al., 2007). Indeed, Charlton et al., (2009) reported a significant correlation between both immediate and delayed memory performance on the Logical Memory test (in addition to other tasks) and FA in the region of the centrum semiovale. There are, however, a number of distinctive characteristics of this study that may account, at least in part, for the differences in findings with the present study. For example, they had a relatively large number

of participants in their study (n = 104 compared to n = 25 in current study) who ranged from 50 to 90 years of age (Charlton et al., 2009) and thus, were substantially older and wider in age range than those studied here. This might have led to a greater variation in white matter microstructure as well as performance on the memory tasks used due to variations in the normal ageing process. Additionally, Charlton et al. (2009) adopted a region of interest approach in their analyses, in which FA was averaged across a number of fibres within a predefined region of interest. This contrasts sharply to the method we used here, in which we examined FA within a single white matter tract.

3.4.2. Conclusions

In summary, although the current significant findings from the standard memory tasks are consistent with the idea that the fornix may be important for recollection but not familiarity memory, we failed to observe a consistent relationship between fornix FA and recall performance across all tasks. It is possible, therefore, that more sensitive memory tasks that provide direct measures of recollection and familiarity are more suited to detecting changes in memory performance associated with variations in fornix white matter microstructure in young healthy populations (e.g. receiver operating characteristic recognition memory tasks as used in conjunction with DTI in Chapter 2). Our findings emphasize the importance of using behavioural tests that are sensitive to and reliably measure the cognitive construct of interest when examining the relationship between individual differences in white matter microstructure and cognitive ability.

3.4.3. Future directions

As already discussed in Chapter 2, this investigation cannot elucidate the causal relationship between episodic memory performance and fornix microstructure. It may be that individuals who innately have greater fornix microstructure have better recollection memory, or just as plausibly, an individual's fornix microstructural integrity may increase over time as their recollection ability improves. To investigate the latter possibility a DTI and memory training

investigation could be carried out, in which individuals undergo DTI neuroimaging before and after behavioural training that is designed to improve episodic memory scores. If training participants does lead to improved episodic memory performance, it may be predicted that an increase in FA of the fornix might be observed. However, if no fornix FA change was observed it might suggest that long-term episodic memory does not lead to plasticity after training and that the relationship between FA and recollection performance is driven by innate differences. In Chapter 5, we begin the process towards such an investigation by carrying out a training study to determine if LTM scores can be improved after extensive spatial working memory training.

Another obvious future study considering investigations such as that by Charlton et al (2010) would be to examine the effect of aging on the FA of the fornix. As a starting point, the fornix FA of young and older adults could be compared to determine if aging leads to changes in microstructure. Any difference in FA could be examined in conjunction with behavioural measures (i.e. on ROC recognition memory tasks) to determine whether the two are inter-related. Notably, this study was originally attempted for the present thesis, with DTI and behavioural data having been obtained from 32 healthy older adults (who also acted as the controls for the patients described in Chapter 4). Unfortunately, however, an unforeseen scanner upgrade took place in between the collection of data in the young participants for Chapter 2 and the older participants, leading to a change in b-value and thus, FA values. This rendered any comparison between the two groups to be invalid and therefore, this data will not be presented in this thesis.

Chapter 4 - An investigation into the effects of medial temporal lobe damage on the resting-state networks and white matter of the brain

4.1. Introduction

Organic anterograde amnesia is a devastating condition that is classically characterised by severe and permanent deficits for the recall of recent events (see section 1.2.2 for further details; Milner, 1972, 2005; Milner et al., 1968; Scoville & Milner, 1957). Whilst the cognitive profile of amnesic individuals with focal MTL lesions has been widely researched, neuroimaging investigations of this population have been relatively limited, consisting predominantly of volumetric quantitative analyses of the lesioned area (Bayley, Gold, Hopkins, & Squire, 2005; Colchester et al., 2001; Gold & Squire, 2005; Squire, Amaral, & Press, 1990). In these volumetric studies, one common approach is for the anatomical landmarks of the cortical and sub-cortical ROIs to be identified on structural MRI images, and then for the ROIs to be delineated by hand and their respective volumes measured. For example, Squire et al (1990) drew on the coronal slices of the T1 structural images of 4 amnesic patients and 12 controls to create area measurements of the hippocampal formation, parahippocampal gyrus and temporal lobe. They found that amnesic patients had significant reductions of their hippocampal formation but not their temporal and parahippocampal gyri in comparison to controls (Squire et al., 1990). Brain normalization techniques are generally employed in volumetric studies to correct for the innate variability in brain size between individuals, without which differences between patients and controls may occur. Gold and Squire (2005)

recently assessed the efficacy of a number of normalization techniques including normalisation by intracranial volume, normalisation by using a standard atlas as a reference, and normalisation by brain region at the level of the anterior commissure. In a group of 5 amnesic patients and 30 controls they found that normalization by intracranial volume was the most effective and reduced volume variability in nearly all brain regions across the brain.

More recently, a handful of VBM and DTI neuroimaging studies have been conducted to investigate the respective grey and white matter damage associated with amnesia. These investigations are often at the whole brain level and therefore, enable a more comprehensive exploration of brain damage in amnesic individuals in comparison to the more limited approach afforded by the use of ROIs in most volumetric quantitative analyses. One grey matter VBM study showed that bilateral hippocampal lesion individuals had prominent grey matter reduction in the bilateral hippocampus, with no grey matter atrophy outside the MTL (Di Paola et al., 2008). Similarly, grey matter VBM of a single severe amnesic also revealed bilateral damage to the hippocampal formation, although at an uncorrected statistical threshold (Cipolotti et al., 2006). Interestingly, white matter VBM research has showed that damage to grey matter structures can impact the white matter tracts to which they are connected. For example, Di Paola et al. (2011) showed a group of amnesic patients had gross white matter reductions to tracts associated with the MTL, for example the fornix, anterior portion of the cingulum bundle, and uncinate fasiculus bilaterally (Di Paola, Moscatelli, Bigler, Caltagirone, & Carlesimo, 2011). DTI work has also revealed similar findings – a recent investigation of 2 amnesic patients with focal thalamic lesions used tractography to trace the mammillo-thalamic tract and found that the mean FA of this tract was significantly reduced in the patients in comparison to controls (Cipolotti et al., 2008).

Functional magnetic resonance imaging (fMRI) investigations of amnesic patients are relatively uncommon. This is primarily because of the rarity of the amnesic condition but also a number of practical considerations. For instance, patients may not be capable of performing an experimental task successfully for the entire time period necessary for fMRI data collection

and often, considerable anxiety can be experienced around entering the MRI scanner. One study asked the famous developmental amnesic Jon, who has a 50% reduction in hippocampal volume, and matched controls to carry out a memory retrieval task in the scanner that consisted of statements about the participants personal autobiographical events and facts or public events and general knowledge (Maguire et al., 2001). Results showed that Jon had a similar pattern of activity during successful memory retrieval as controls in a network of regions associated with mnemonic function (i.e the hippocampus, retrosplenial cortex, parahippocamal gyrus, temporal lobe and frontal cortex), with the main difference being that Jon's activations were bilateral whilst controls were unilateral. The authors indicated that these results suggest that damaged tissue can retain functionality and that bilateral activations may be important indicators of disordered memory (Maguire et al., 2001). Another single case fMRI study focused on an amnesic with bilateral MTL damage, who has an intact ability to retrieve spatial information (i.e. spatial layouts of previously experienced environments) but poor episodic memory. This study reported preserved activity in the parahippocampal cortex but not the hippocampus, suggesting that the former supported the patient's ability to retrieve spatial information, with the latter being indicative of impaired episodic memory (Rosenbaum, Winocur, Grady, Ziegler, & Moscovitch, 2007). Finally, a very recent fMRI investigation found that a patient with 50% bilateral hippocampal damage demonstrated significant activity in the residual cortex of the right hippocampus whilst successfully carrying out a scene construction task in the scanner (Mullally, Hassabis, & Maguire, 2012). The authors concluded that a preserved ability to carry out scene construction in amnesia is crucially supported by remaining function in the damaged hippocampi (Mullally et al., 2012). Although all single case studies, the aforementioned fMRI studies importantly reveal that damaged tissue can retain function and that hippocampus activity can persevere even when memory is disrupted.

Examining the extent of grey and white matter damage in focal amnesic cases, as well as investigating the functional impact of MTL damage, has become increasingly important to theoretical debates of MTL function. For example, a key issue in the MTL-perception debate is

whether visual discrimination deficits in amnesia can be attributed to MTL structures, or whether these impairments are, in fact, the result of damage to regions beyond the MTL that are more traditionally associated with perceptual processing. To address this issue, Lee and Rudebeck (2010) carried out volumetric measurements and fMRI on 2 patients, HC3 and MTL3, who have previously taken part in a number of investigations of visual discrimination (e.g. Barense et al., 2007; Lee, Buckley, et al., 2005). A volumetric analysis of their MTL regions, and lateral temporal lobes revealed that patient HC3 has damage constrained bilaterally to the hippocampus, whilst MTL3 has more extensive bilateral damage to all of the MTL structures, the right anterior fusiform gyrus, temporopolar cortex and anterior lateral temporal cortex (Lee & Rudebeck, 2010b). fMRI was also conducted as patients HC and MTL3 and their controls completed a functional localizer task in which they monitored images of faces, scene and objects and scrambled versions of these images within the scanner. Results showed that both individuals had appropriate activations within extrastriate cortical areas that are believed to be important for the perception of scenes, faces and objects (Lee & Rudebeck, 2010b), more specifically the parahippocampal place area (Epstein & Kanwisher, 1998), the fusiform face area (Kanwisher, Mcdermott, & Chun, 1997) and the lateral occipital complex (Malach et al., 1995). These findings undermine the suggestion that these amnesic patients' visual discrimination deficits may be explained by damage or dysfunction beyond the MTL (Levy et al., 2005; Shrager et al., 2006; Suzuki, 2009).

Although the findings of Lee and Rudebeck (2010a) suggest that Patient HC3 and Patient MTL3 do not possess grey matter damage and dysfunction to visual cortical regions, it is critical to note that they do not speak to the possibility of disrupted functional connectivity between brain areas or white matter atrophy at the whole brain level. Indeed, to date, studies of MTL function in patients with focal lesions have not examined the potential impact of MTL damage to functional and structural connectivity throughout the brain. This is an important issue because the brain is made up of numerous functional neural networks in which anatomically segregated brain regions are connected via fiber pathways. Cognitive deficits

following MTL damage may, therefore, result from negative knock-on effects on regions and connections beyond the MTL. To investigate this, the current study used resting-state fMRI (Rs-fMRI) and diffusion tensor imaging (DTI) to examine the integrity of functional resting-state networks and white matter connectivity in patients HC3 and MTL3. Rs-fMRI and DTI are ideal neuroimaging techniques to use in clinical populations because, unlike fMRI, they do not require the participant to actively take part in any tasks within the scanner and require relatively shorter scanning times. Although, to our knowledge, no previous study has investigated the effect of focal MTL lesions on both resting-state networks (RSNs) and white matter integrity of the brain, there has been considerable work in this area in Alzheimer's disease (AD), and mesial temporal lobe epilepsy (mTLE). Since these neurological conditions are associated with structural damage to the MTL regions and mnemonic deficits, Rs-fMRI and DTI findings in AD and mTLE may provide some indication of how MTL damage in focal amnesic cases may impact brain connectivity. We will therefore review Rs-fMRI and the RSNs of interest before discussing the Rs-fMRI and DTI findings in mTLE and AD.

4.1.1. Resting-state fMRI (Rs-fMRI)

The brain is constantly metabolically and functionally active even when it is not processing a specific input or generating an output. Indeed this innate neuronal activity represents around 95% of the brains energy consumption (Raichle & Mintun, 2006). Biswal and colleagues (1995) were the first to recognize that this innate activity could be measured in spontaneous low frequency BOLD signals, and these signals were temporally correlated in two functionally related areas, the left and right sensorimortor motor cortices. Although there was early concern that these findings were not legitimate, they were soon replicated (Lowe, Mock, & Sorenson, 1998; Xiong, Parsons, Gao, & Fox, 1999). Following a decade of research, the BOLD signal fluctuations occurring at low frequencies (< 0.1 Hz) are now considered to be related to the resting baseline activity of the brain. These fluctuations are specifically organized into spatially distributed large-scale networks within the brain that share a common time-course of low-frequency BOLD signal fluctuations and are termed 'resting-state networks' (RSNs;

Beckmann, DeLuca, Devlin, & Smith, 2005; De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006; Greicius et al., 2003). These RSNs are thought to represent known functional networks because temporal fluctuations are observed between brain areas that are known to support specific cognitive functions (Cordes et al., 2000).

RSNs are consistently found using a number of analysis techniques (Damoiseaux et al., 2006; Greicius, Srivastava, Reiss, & Menon, 2004; Zuo et al., 2010) and are stable between subjects (Beckmann et al., 2005; Damoiseaux et al., 2006; S. M. Smith et al., 2009) and sessions (Chen et al., 2008). Fascinatingly, these set of co-activating functional systems are also found at different levels of consciousness, (Boly et al., 2009; Greicius et al., 2008), stages of cognitive development (Fransson et al., 2007), and across species (Kannurpatti, Biswal, Kim, & Rosen, 2008; Vincent et al., 2007). Rs-fMRI analyses can be data driven (for example via the use of independent component analysis (ICA); McKeown et al., 2003; Beckmann et al., 2005) so that no a priori assumptions or ROIs are applied to the data to derive the RSNs, or, Rs-fMRI analyses can be model-driven (for example, via the use of seed-based correlation analysis; Biswal et al., 1995).

The RSNs most commonly identified from both ICA or ROI-based analysis are the medial visual cortical network (MVN), lateral visual cortical network (LVN), auditory network (AUN), sensory-motor network (SMN), executive control network (ECN), default mode network (DMN), and left and right fronto-partietal network (lFPN and rFPN) (Beckmann et al., 2005; Damoiseaux et al., 2006; S. M. Smith et al., 2009). Trachtenberg and colleagues (2011) also recently suggested two hippocampal networks are also observable, the anterior hippocampal network (AHN) and the posterior hippocampal network (PHN; see Figure 4-1).

The MTL structures are implicated in 3 RSNs. Firstly, the default mode network (DMN) encompasses the prefrontal, cingulate, lateral parietal, cerebellar areas, inferior/middle temporal gyri, thalamic nuclei and MTL regions (Boly et al., 2008), and is so called because this network is engaged under resting condition and de-activated when the participant is involved with an active task (Shulman et al., 1997). This component, however, is also engaged in the

performance of active tasks and is specifically implicated in cognitive functions such as, working memory (Esposito et al., 2006) and the consolidation of episodic memory (Greicius et al., 2004). Two other RSNs have also recently been found within the MTL, the PHN, which encompasses the bilateral portions of the posterior hippocampus, parahippocampal gyrus, thalamus, lingual gyrus, precuneus, amygdala, temporal pole and brainstem, and the AHN, with consists of the bilateral portions of the anterior hippocampus and parahippocampal gyrus, amygdala, temporal fusiform cortex, temporal pole, and orbital frontal cortex (Trachtenberg et al., 2011). Whilst very little is known about these two RSNs, there has been work suggesting a functional distinction between the anterior and posterior portions of the human MTL (e.g Chua, Schacter, Rand-giovannetti, & Sperling, 2007; Köhler, Crane, & Milner, 2002; Litman, Awipi, & Davachi, 2010; Mullally et al., 2012). A recent investigation also showed that PHN and AHN connectivity were effected differentially in APOE-ε4 and APOE-ε2 carriers, alleles that are thought to make individuals vulnerable or protected from Alzheimer's disease respectively (Trachtenberg et al., 2011).

In brief, beyond the MTL-related RSNs: the MVN incorporates the primary visual areas found in the calcarine sulcus, the cuneus and portions of the lingual gyrus, whilst the LVN consists of the lateral occipital cortex, lingual gyrus and temporal-occipital fusiform cortex. The SMN includes the primary sensory motor cortices, the sensorimotor areas and the supplementary motor area. The auditory network (AUN) consists of the primary auditory cortex, planum temporale (Wernicke's area), planum polare, Broca's area, insular, opercular cortex and the thalamus. ECN incorporates the anterior cingulate cortex bilaterally, paracingulate cortex, frontal pole, inferior and middle frontal gyri in the PFC, and portions of the pre and post-central gyri. Finally, the left frontal-partietal network (lFPN) incorporates the lateral occipital cortex, lateral parietal regions, the inferior and middle temporal gyri, frontal orbital cortex, frontal opercular cortex, and the inferior and middle frontal gyri, with the right

frontal-parietal network (rFPN) being the right hemisphere homologue of the lFPN.

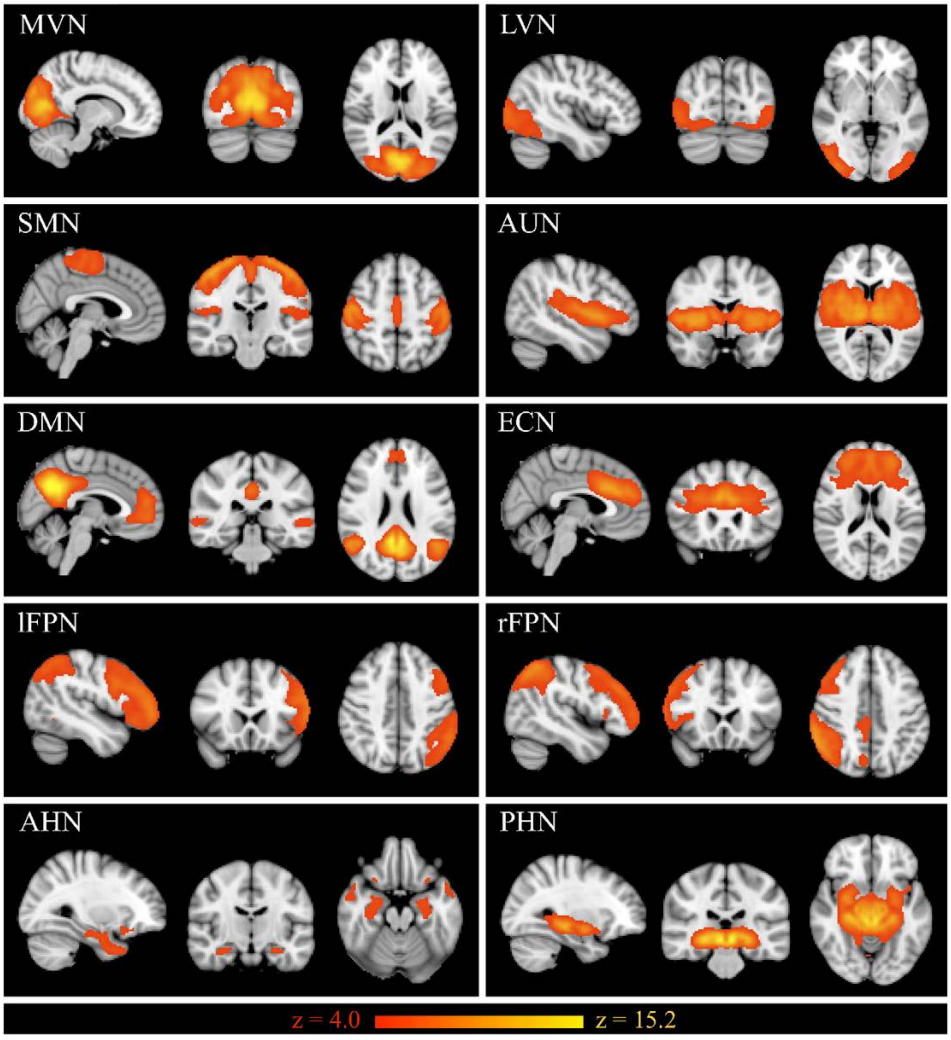

Figure 4-1: The common sets of RSNs identified from a group of 77 subjects. All images are present in MNI space. Taken from Trachtenberg et al (2011).

4.1.2. RS-fMRI in mTLE and AD

Rs-fMRI investigations have detected subtle functional abnormalities in brain networks thought to support complex cognitive processes in AD and mTLE patients. mTLE is the most common form of intractable human epilepsy, and is characterised by epileptogenic activity arising from the MTL, most commonly the hippocampus. Pathological damage to the epileptogenic hippocampus, termed hippocampal sclerosis (HS), is found in a large number of mTLE patients, (Keller et al., 2002; Bonilha et al., 2004) and is associated with memory (Del Vecchio, Liporace,

Nei, Sperling, & Tracy, 2004) and language impairments (Adcock, Wise, Oxbury, Oxbury, & Matthews, 2003). ICA analysis of Rs-fMRI data has shown that mTLE with HS individuals have decreased co-activation within the DMN regions in comparison to controls, in particular the dorsal mesial PFC, mesial temporal lobe and inferior temporal cortex (Z.Zhang et al., 2010). In addition, decreases in connectivity within the AUN, SMN (Z. Zhang, Lu, Zhong, Tan, Liao, et al., 2009) and the 'dorsal attention network' (a homologue of the lFPN and rFPN; Z. Zhang, Lu, Zhong, Tan, Yang, et al., 2009) have also been found, with a contrasting increase in functional connectivity within the primary visual cortex (a homologue to the MVN; Z. Zhang, Lu, Zhong, Tan, Liao, et al., 2009). These results suggest that mTLE is a neural network disease that affects widespread brain networks possibly due to the propagation of seizures from the epileptogenic zone to distant brain regions (Spencer, 2002). It also suggests that in mTLE, RSN dysfunction may play a role in the cognitive deficits in attention and auditory/somatosensory perception (Allegri, Drake, & Thomson, 1999) as well as the more typical ones in memory (Z. Zhang, Lu, Zhong, Tan, Yang, et al., 2009; Z. Zhang, Lu, Zhong, Tan, Liao, et al., 2009; Z. Zhang et al., 2010).

AD is a progressive degenerative dementia that is characterized by widespread cortical changes, loss of neurons and neurofibrillary tangles (Braak, Alafuzoff, Arzberger, Kretzschmar, & Del Tredici, 2006; Braak & Braak, 1996). Atrophy of the bilateral hippocampus and MTL structures are seen in the prodromal stage of the disease, amnestic mild cognitive impairment (MCI; Jack et al., 1999; Du et al., 2001; Whitwell et al., 2007) and is associated with EM impairment (Petersen et al., 1999; Petersen, 2004). As AD progresses, pathological atrophy is observed to regions beyond the MTL, such as the temporal, parietal and frontal lobes (Frisoni et al., 2002; Buckner et al., 2005; Whitwell et al., 2007) and this is associated with additional cognitive deficits for example, in attention or language (e.g Grady et al., 1988; Perry & Hodges, 1999; Welsh, Butters, Hughes, Mohs, & Heyman, 1992). Rs-fMRI studies of MCI and AD patients, using a range of analysis techniques, have consistently shown reductions in co-activation of regions within the DMN in comparison to healthy controls (Agostini et al., 2011; Bai et al., 2008; Greicius et al., 2004; H. Y. Zhang et al., 2010; Zhou et al., 2010). This

contributes to the converging evidence that a network of brain regions within the DMN is particularly effected by the disease process, such as, atrophy (Buckner et al., 2005; Frisoni et al., 2002) and amyloid deposits (Buckner et al., 2005; Klunk et al., 2004). Interestingly, enhanced connectivity within RSNs of the frontal lobe have also been found in AD (Agostini et al., 2011; Supekar, Menon, Rubin, Musen, & Greicius, 2008; Wang et al., 2006; H. Y. Zhang et al., 2010; Zhou et al., 2010) - a recent investigation demonstrated that co-activation of regions within the ECN was enhanced in AD, and that this connectivity was positively correlated with the patients' executive and language psychometric scores (Agosta et al., 2012). This converges with previous task-based fMRI studies that demonstrates increased frontal, posterior parietal and cingulate cortex activations in MCI patients whilst they engage in preserved semantic memory tasks (Woodard et al., 2009), and supports the hypothesis that as the temporal lobes become increasingly pathological (leading to reduced DMN connectivity) increased frontal lobe connectivity or activity represents a compensatory mechanism to support cognitive functioning in AD individuals (Agosta et al., 2012).

4.1.3. DTI in mTLE and AD

DTI investigations of mTLE patients with HS at the whole brain level have most consistently revealed reductions in FA in the pathological hippocampus (Assaf et al., 2003; Hugg, Butterworth, & Kuzniecky, 1999), and the contralateral hippocampus (Assaf et al., 2003; Londoño, Castillo, Lee, & Smith, 2003). Studies investigating the fornix have only found significant FA reductions in mTLE patients with HS after adopting an ROI approach. For instance, by carrying out fornix tractography and then extracting its mean FA (Concha et al., 2005, 2009; Voets et al., 2009) or by creating an ROI of the fornix and conducting TBSS within this region (Nguyen et al., 2011). The uncinate fasciculus (UF), a fiber tract that connects the cortical areas in the ventro-medial and polar regions of the temporal lobes to the frontal cortical areas, has also been investigated in mTLE individuals. Microstructural white matter damage to this tract has been associated with episodic LTM impairment in individuals with schizophrenia (Nestor et al., 2008) and traumatic brain injury (Niogi et al., 2008). In mTLE,

microstructure reductions in the right and left UF were only revealed following probabilistic tractography (Voets et al., 2009) or by applying a whole hemisphere mask (Nguyen et al., 2011). This has led to the suggestion that focal lesions within the MTL may lead to subtle changes in white matter tracts that are only detectable after applying ROIs (Nguyen et al., 2011).

DTI studies of AD patients in comparison to controls most consistently show decreased FA in regions of the MTL, such as the hippocampus, entorhinal cortex and parahippocampal gyrus (Choo et al., 2010; Fellgiebel et al., 2004; Fellgiebel & Yakushev, 2011; Salat et al., 2010), the temporal lobes (Takahashi et al., 2002; Naggara et al., 2006) and the posterior cingulum (Choo et al., 2010; Fellgiebel et al., 2008), with inconsistent findings in regard to the frontal and parietal lobes (Fellgiebel et al., 2004; Medina et al., 2006; Salat et al., 2010). White matter changes are also seen in the fiber tracts of the MTL with a decrease in FA in the fornix of AD patients (Hattori, Sato, Aoki, Yuasa, & Mizusawa, 2012; Huang et al., 2012; O'Dwyer et al., 2011) but not, however, in MCI cases (O'Dwyer et al., 2011). Changes in the white matter integrity of the UF have also been found in AD, for example, recent TBSS and tractography studies showed a reduction in UF FA in AD individuals (Damoiseaux et al., 2009; Fujie et al., 2008).

In the current study, we aimed to compare the RSNs of patients HC3 and MTL3 with that of neurologically healthy control participants using an ICA approach. Considering the lesions of patient HC3 and patient MTL3, and the existing mTLE and AD literature, it was predicted that both patients may have decreased connectivity within the RSNs that encompass the MTL structures, namely the DMN, AHN and PHN. Moreover, it is possible that changes beyond the MTL RSNs may also be seen, for example, increased frontal activity within the ECN. To investigate potential differences in white matter, whole brain white matter VBM and DTI analyses were conducted. The latter involved voxel-wise statistical analysis (i.e. TBSS) at the whole brain level as well as on ROIs of the fornix, and the right and left UF. It was predicted that both patients MTL3 and HC3 will have considerable macro and microstructure reductions

in fornix, whilst patient MTL3, who has anterior temporal lobe damage, may have additional reductions in the UF.

4.2. Methods

4.2.1. Participants

This research received ethical approval from the Oxfordshire Research Ethics Committee (07/H0604/115; 08/H0606/133) and all subjects gave informed written consent prior to taking part. Two patients underwent neuroimaging. Patient HC3 has been previously identified using qualitative visual ratings as having predominant HC damage (see Figure 4-2 (B); female, age = 51 years and 11 months, education = 10 years), and patient MTL3 has a larger MTL lesion including the HC and PRC (see Figure 4-2 (A); patient MTL3, female, age = 65 years and 7 months, education = 10 years) (Lee et al., 2005). Patient HC3 suffered carbon monoxide-induced hypoxia and standard neuropsychological assessment demonstrates intact semantic memory (Category Comprehension: 64/64; Pyramids and Palm Trees: 51/52) but poor episodic memory recall (Logical Memory immediate recall: 14/75; delayed recall: 7/50; Rey-Osterrieth Complex Figure delayed recall: 3/36) and impaired recognition memory for prose (Logical Memory recognition: 19/30) but not scenes or faces (Warrington Recognition Memory Test scenes: 26/30; faces: 44/50). Patient MTL3 is a viral encephalitis patient who possesses severe episodic memory recall (Logical Memory immediate recall: 10/75; delayed recall: 2/50; Rey-Osterrieth Complex Figure delayed recall: 4.5/36) and recognition deficits (Logical Memory recognition: 18/30; Warrington Recognition Memory Test scenes: 13/30, faces: 30/50) as well as a mild semantic memory impairment (Category Comprehension: 54/64; Pyramids and Palm Trees: 46/52).

For the Rs-fMRI and DTI investigations, the patients were compared to 32 participant control group that were age and education matched (female = 17, mean age = 56.67, age standard deviation = 6.45, mean education = 15.03 years, standard deviation education = 4.58). There was no significant difference between each patient and the control group in terms of age

or years of education ($p > 0.08$).

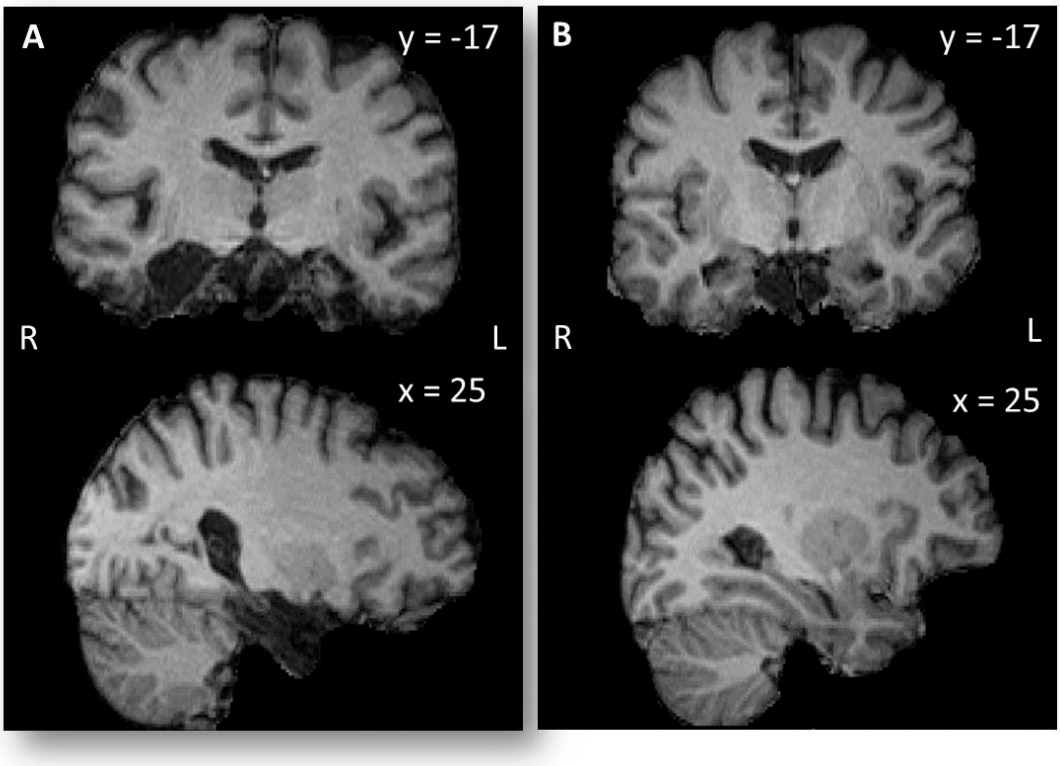

Figure 4-2: Structural T1 images of: (A) patient MTL3 who has gross bilateral MTL damage which is most extensive in the right hemisphere, and (B) Patient HC3 who has bilateral damage to the hippocampi but no other region of the MTL.

4.2.2. Psychometric assessment

All control subjects were screened for the early signs of memory loss using the Addenbrooke's Cognitive Examination revised test (ACE-R) (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006). This is a short but sensitive cognitive battery used to screen for those in the early stages of dementia, which can also differentiate between different subtypes of dementia, such as MCI, frontotemporal dementia and AD (Mioshi et al., 2006). Administration takes roughly 15 minutes and 5 cognitive domains are tested and scored accordingly: memory (0-26), verbal fluency (0-14), attention/orientation (0-18), visuo-spatial (0-16) and attention/orientation (0-

18). The points from each 5 domains are then added together to give the maximum score of 100. A high exclusion cut off was adopted of $\leq$ 88, which gives 94% sensitivity and 89% specificity of dementia. None of our controls were excluded based on this criterion.

4.2.3. Imaging data acquisition, preprocessing and analyses

Participants were scanned using a 3-T Siemens Trio scanner with a 12 channel head coil at the University of Oxford for Clinical Magnetic Resonance Research. For the Rs-fMRI whole-brain functional imaging data was acquired using a gradient echo planar imaging (EPI) (TR =2,000 ms, TE =28 ms, flip angle = 89^{o}, resolution=3x3x3.5 mm, acquisition time = 6 min 4s). During this scan participants lay in dim light with their eyes open and were asked to think of nothing in particular, but to not fall asleep. The DTI dataset consisted of 60 volumes, with diffusion weighting isotropically measured along 60 directions using a b-value of 1000 s/mm^2 (65 slices; voxel size 2.0 x 2.0 x 2.0mm; repetition time [TR] = 9.3s; echo time [TE] = 94 ms; acquisition time = 10 min 30 s). Three volumes without diffusion weighting (b = 0 s/mm^2) were also collected throughout the sequence. The structural T1-weighted images were acquired using a FLASH sequence (TR = 11.2 ms; TE = 4.7 ms; flip angle = 8^{o}, voxel size = 1.0 x 1.0 x 1.0mm). All image preprocessing and analyses were carried out using tools from the FMRIB Software Library (FSL, www.fmrib.ox.ac.uk/fsl).

4.2.4. Functional MRI at rest (Rs-fMRI)

Rs-fMRI data analyses were conducted using a methodology based on previously published work (Filippini et al., 2009). In brief, preprocessing of each Rs-fMRI dataset included motion correction, brain extraction, spatial smoothing using a Gaussian kernel of full-width half maximum 6 mm, and temporal filtering with a high-pass filter of 150 s. Because of the extensive lesions in our two patients, particular care was devoted to the registration process. Functional data were aligned to structural images (within-subject) initially using linear registration (FMRIB's Linear Image Registration Tool, FLIRT; http://fsl.fmrib.ox.ac.uk/flirt/), and then optimized using the Boundary-Based Registration approach (Greve & Fischl, 2009).

Structural images were transformed to standard space (Montreal Neurological Institute, MNI, 152 template) using a non-linear registration tool (FMRIB's Non-linear Image Registration Tool, FNIRT; http://fsl.fmrib.ox.ac.uk/fnirt/), and the resulting warp fields were applied to the functional statistical summary images. Moreover, to ensure the lesions of the patients did not contribute to registration problems between their Rs-fMRI and structural scans (Brett et al., 2001), cost function masking was applied (Andersen, Rapcsak, & Beeson, 2010; Brett, Leff, Rorden, & Ashburner, 2001). First, a mask was created for each patient's lesion by drawing around the lesion outline on the patients' structural MRI scans. The resulting masks were then applied during the registration of each patient's structural scan to standard space using FNIRT.

After preprocessing, the Rs-fMRI data from the 32 controls were concatenated into a single 4D data set and analyzed using probabilistic ICA as implemented in Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC, http://fsl.fmrib.ox.ac.uk/melodic/ for details see Beckmann et al., 2005). This defined fifty-two components representing group-averaged networks of brain regions with temporally correlated BOLD signal. Seven RSNs of interest were then selected on the basis of spatial correlation against a set of previously defined maps (Beckmann et al., 2005), with an eighth RSN the PHN recently described by (Trachtenberg et al., 2011). The remaining components reflected BOLD signal drift, white matter and motion artifacts, and were therefore discarded.

The dual-regression method (Filippini et al., 2009) was used to the compare the resting functional connectivity of each patient with that of controls. First, the full set of ICA spatial maps identified in the control group using ICA were used in a linear fit (spatial regression) against the pre-processed fMRI data set of each individual to create matrices describing temporal dynamics for each component in each participant. These temporal matrices were then used in a second linear model fit (temporal regression) against the preprocessed fMRI data set of each individual. This step produced a statistical parametric map for each component for each subject, describing the extent to which each voxel was involved in each component. The single subject component maps were then collated into 4D files (one for each RSN of

interest, with the 4th dimension being subject identification) and any differences between each patient and the control group were investigated using non-parametric permutation-based testing (5000 permutations; T. E. Nichols & Holmes, 2002) as implemented in randomize (http://fsl.fmrib.ox.ac.uk/randomise). A general linear model (GLM) implemented the following t-test contrasts: patient MTL3 > controls, patient MTL3 < controls, patient HC3 > controls and patient HC3 < controls. These contrasts identified any significant differences in functional connectivity within each RSN, as well as any differences in functional connectivity between each RSN and regions in the rest of the brain. Due to our single case approach, we used a relatively low Z-score (1.7) to threshold the resultant voxel-wise maps. Significant clusters were then identified using a family-wise-error (FWE) corrected cluster threshold of $p < 0.05$.

4.2.5. White matter voxel-based morphometry (VBM)

To investigate if there were differences in gross white matter morphology between HC3 and MTL3 and the control group, VBM (Ashburner & Friston, 2000) of white matter was carried out on the T1-weighted structural images. Firstly, the T1-weighted structural images first underwent brain extraction (S. M. Smith, 2002) followed by tissue type segmentation (Y. Zhang et al., 2001). The resulting white-matter partial volume images were then warped to Montreal Neurological Institute 152 space using nonlinear registration. Registered images were then modulated using the warp field to correct for local expansion or contractions and then smoothed with an isotropic Gaussian kernel (FWHM 2mm). Randomize was then used to carry out permutation-based non-parametric testing and implement the GLM's and statistical thresholding described above for Rs-fMRI analysis.

4.2.6. Diffusion tensor imaging (DTI)

Two complementary techniques were used to analyze the DTI data. The first, tract based spatial statistics (TBSS), carries out voxel-wise statistical comparison between individual subjects' FA maps (for full methodology see, S. M. Smith et al., 2006). This technique allow us to investigate if there were any FA, white matter microstructure differences between the patients HC3 and

MTL3 and controls at the whole brain level. Then to improve statistical power, 2 skeleton-based regions of interest (ROI) were also conducted of two major efferents of the MTL and temporal lobes, the fornix and the right and left UF. The fornix and UF ROI's were created on the basis of tractography in each individual and then combining these outputs to create a standard mask in common space (see next two paragraphs). These fornix and right and left UF masks were then binarised and skeletonized prior to TBSS analysis. The same nonparametric permutation testing (5,000 permutations) and contrasts as the Rs-fMRI described above were then implemented.

An alternative approach to TBSS, that allows investigation of specific white matter tracts, is multi-fiber probabilistic tractography (Behrens, Woolrich, et al., 2003). A different method to those described in Chapter 2 and 3 was adopted to trace the fornix and UF in an effort to improve tract size consistency across participants and reduce the need for manual editing. A slightly modified method previously described in Voets et al. (2009) and Ringman et al. (2007) was implemented to trace the fornix and left and right UF in controls and patients. For the fornix the highest FA voxel within the fornix was used as the seed for probabilistic tractography. The resulting tracts were thresholded at 90% to ensure only paths within the fornix were included. Briefly, to trace the right and left UF, in each participant's FA map the left and right UF were identified and a seed mask consisting of 3x3x3 voxels was drawn on the posterior curve of the pathway. To prevent false-positive tracts traversing the sylvian fissure and fimbria-fornix routes, exclusion masks were drawn along the sylvian fissure and on one coronal slice of the anterior hippocampus. These tracts were then thresholded at 10 % of the resulting pathways.

A unique method was then carried out to combine each individual pathways together in common space, thus creating standard fornix and left and right UF masks across both patients and the controls (these were used as the TBSS mask as described above) which were subsequently applied back in individual native space. This involved the following steps; (1) each participant's thresholded fornix/UF tracts were linearly registered to their structural image (FMRIB's Linear Image Registration Tool; FLIRT) and then optimized using boundary based

registration (Greve & Fischl, 2009); (2) these tracts in structural space were then transformed to standard space using FMRIB's non-linear registration tool (FNIRT); (3) standard space tracts were then combined across all participant's and thresholded at a 25 % for the fornix and 75 % for the UF (i.e. tracts that were in 25 % and 75% of participants remained); (4) these standard space paths that were representative of 25 % and 75 % of participants were then backprojected to each subjects standard image and individual FA map by reversing steps 1 and 2; (5) each individual's fornix and UF tracts were applied to the participants FA map and mean FA values were then extracted. Patient's mean FA were then compared to the controls using a modified t-test for contrasting an individual score to small sample (Crawford & Howell, 1998).

4.3. Results

4.3.1. Rs-fMRI

Using independent component analysis (ICA), eight resting-state networks (RSN) were identified in the Rs-fMRI data and explored further. These included 7 RSNs described by (Beckmann et al., 2005), namely, the medial visual network (MVN), lateral visual network (LVN), sensorimotor network (SMN), default-mode network (DMN), auditory network (AUN), left fronto-parietal network (lFPN), and the right fronto-parietal network (rFPN), and 1 RSN identified (Trachtenberg et al., 2011) termed the posterior hippocampal network (PHN) (Figure 4-3).

In all our imaging analyses, we used a non-parametric permutation-based approach to compare each patient with the control group. Voxel-wise comparisons revealed no significant differences in functional connectivity between patient HC3 and the control group in any of the identified RSNs. In contrast, a decrease in functional connectivity was observed in patient MTL3 compared to controls in relation to the PHN. There was a significantly decreased degree of co-activation between regions that comprise the PHN, in particular the parahippocampal cortex, posterior hippocampus and thalamus in the right hemisphere, as well as significantly decreased functional connectivity between the PHN itself and regions beyond this RSN, including the right

insular cortex, planum temporale, middle temporal gyrus and inferior lateral occipital cortex, and the bilateral anterior and posterior cingulate gyri (see Figure 4-4). There were no other significant differences between patient MTL3 and the control group in any of the other identified RSNs.

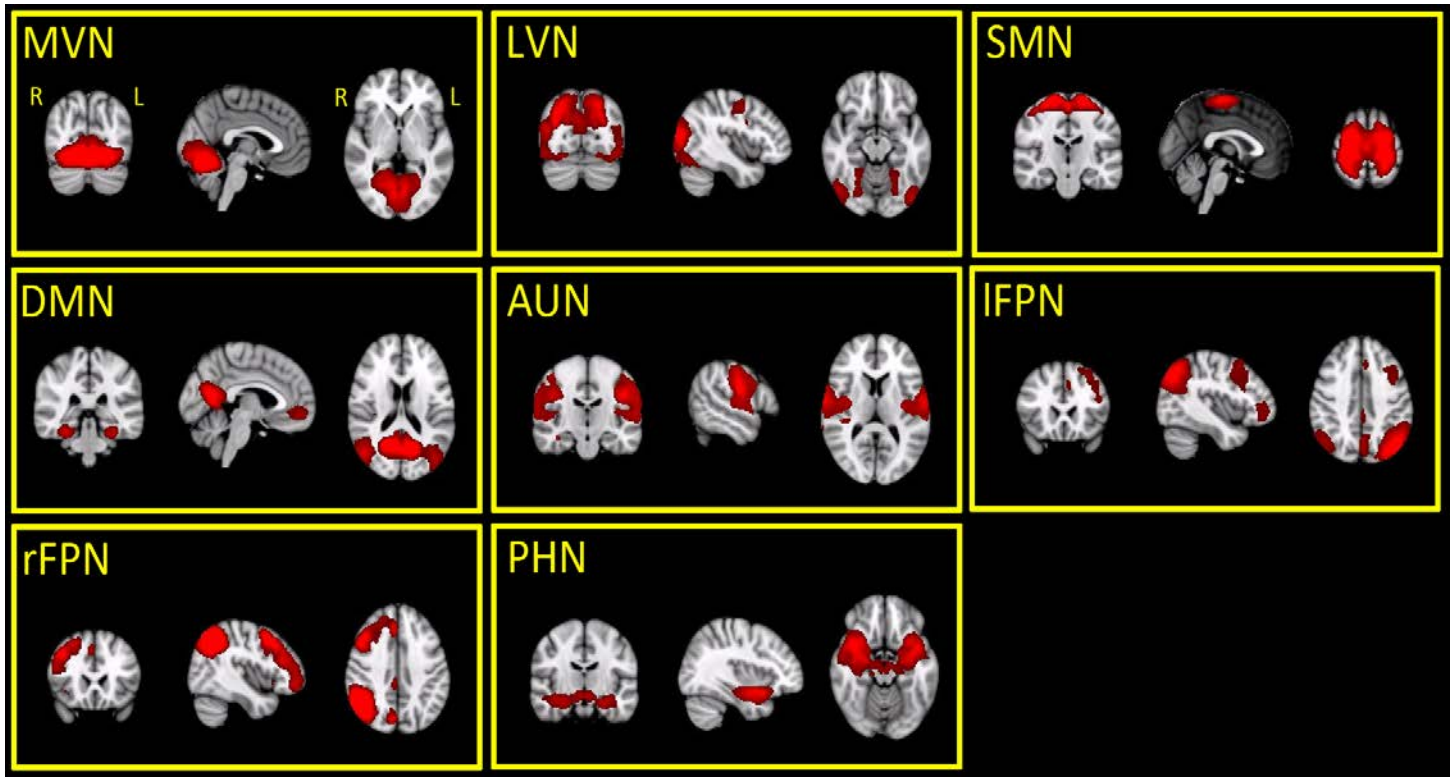

Figure 4-3: The 8 RSNs identified in the control group (activity rendered on MNI152 template; R = right, L = left). All RSN activity maps were created using a statistical threshold of z = 2.3, cluster corrected p < 0.05, and further thresholded at different z-scores for display purposes. Key: MVN = medial visual network; LVN = lateral visual network; SMN = sensorimotor network; DMN = default-mode network; AUN = auditory network; lFPN = left fronto-parietal network; rFPN = right fronto-parietal network; PHN = posterior hippocampal network.

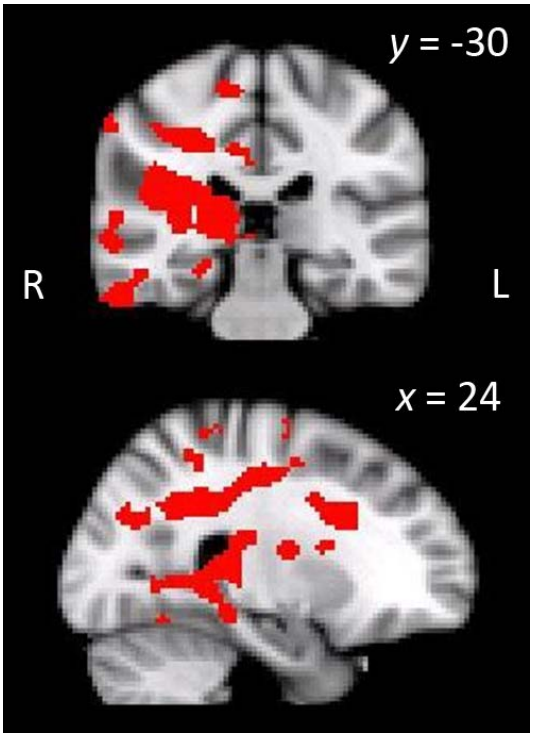

Figure 4-4: Significantly lower degree of co-activation between regions within the PHN, and between the PHN and areas beyond this network in Patient MTL3 (activity rendered on MNI152 template, cluster corrected p < 0.05; R = right, L = left).

4.3.2. White matter VBM

To investigate any differences in gross white matter morphology between each patient and the control group, VBM (Ashburner & Friston, 2000) of white matter was carried out on the participants' T1-weighted structural images. This revealed that there was a trend towards a significant decrease in white matter in patient MTL3 throughout the MTL and fornix bilaterally, the right thalamus and the left and right temporal poles (corrected p = 0.059, cluster 1 voxels = 11038, x= 42, y = 0, z = -46, cluster 2 voxels = 118, x = 60, y = -18, z = -8; Figure 4-5). There were no other differences between patient MTL3 and the controls (in particular in posterior occipital and temporal regions), nor were there any significant differences between patient HC3 and the control group.

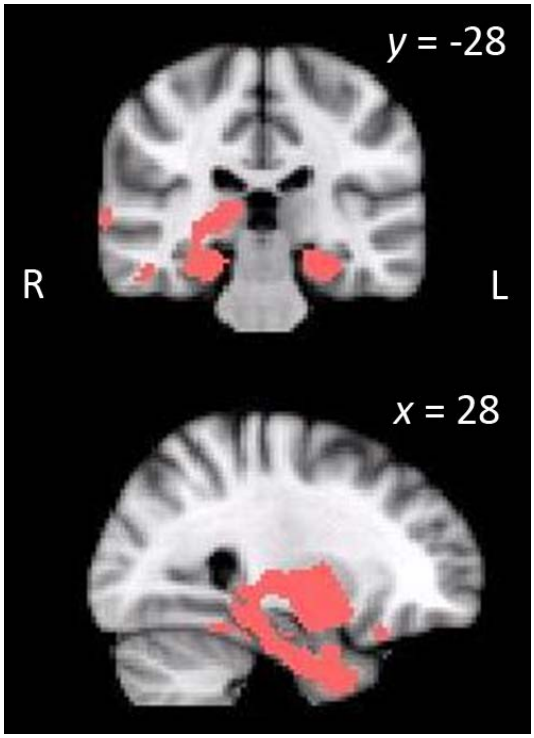

Figure 4-5: Gross white matter differences between Patient MTL3 and controls as revealed by white matter VBM (rendered on MNI152 template, cluster corrected p < 0.06; R = right, L = left).

4.3.3. TBSS

Whole brain TBSS showed that there were no significant increases or decreases in FA between either patient MTL3 and HC3 and controls. For the ROIs, the contrast 'MTL3<Controls' revealed significantly decreased FA in MTL3's fornix (corrected p = 0.05; cluster 1 voxels = 62, x = 0, y = -5, z = 11; cluster 2 voxels 13, x = 0, y = -2, z = 7; cluster 3 voxels = 11, x = 1, y = 1, z = 1; Figure 4-6 (A) and the right UF (corrected p = 0.02; cluster 152 voxels, x = 37; y = 11, z = -35; Figure 4-6 (B), but not the left UF in comparison to controls. The contrast 'HC3<Controls' indicated a trend towards a decrease in patient HC3's fornix FA in contrast to controls (corrected p = 0.059; cluster 1 voxels = 71, x = 0, y = -5, z = 11; cluster 2 voxels = 21, x = 3, y = -18, z = 15) but not for either the left or right UF FA. Otherwise, the contrasts 'MTL3 > Controls' and 'HC3 > Controls' showed no other significant clusters for the fornix or UF ROIs.

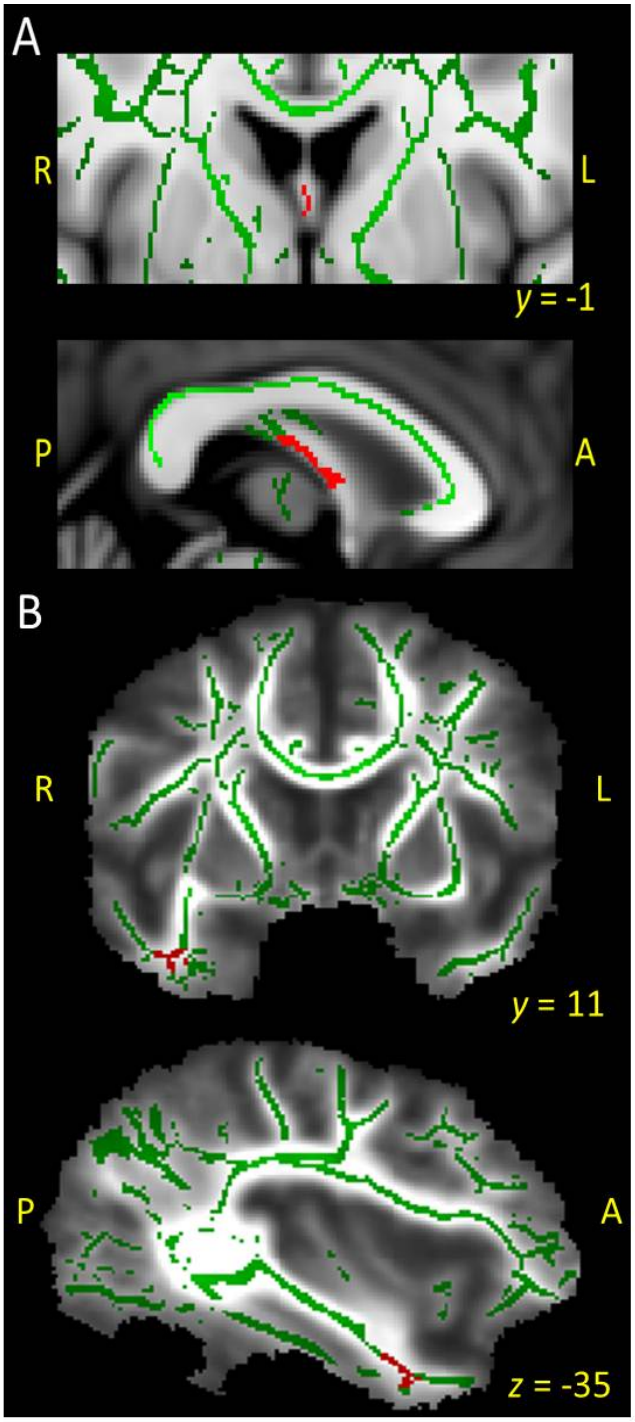

Figure 4-6: (A) Significant reduction in FA in the fornix of patient MTL3 (shown in red) in comparison to controls (cluster corrected p < 0.05 fornix ROI); (B) Significant reduction in FA in the right UF of patient MTL3 (shown in red) in comparison to controls (cluster corrected p < 0.05 right UF ROI).

4.3.4. Tractography

The fornix tractography results converged with the TBSS findings, with MTL3's fornix mean FA significantly less than the controls ($t(31) = -2.051$; $p = 0.02$), whereas HC3 showed a trend towards a reduction in mean fornix FA in comparison to controls ($t(31) = -1.93$; $p = 0.06$). For the right UF, MTL3's mean FA was significantly less than controls ($t(31) = 0.19$; $p = 0.00001$), whereas her left UF mean FA was not ($t = -1.37$; $p = 0.18$). HC3's left and right UF mean FA did not significantly differ from the controls (both $p > 0.4$).

4.4. Discussion

This explorative investigation of the RSNs and white matter tracts of two amnesic patients was conducted using Rs-fMRI, VBM and DTI. Patient MTL3, who has gross bilateral damage to the MTL, has decreased co-activation of brain regions within and beyond the PHN, a trend towards a reduction in gross white matter morphometry of the bilateral MTL, with additional microstructural white matter reductions to two major tracts of the MTL and temporal lobes, the fornix and the right UF. On the other hand, patient HC3, whose damage is constrained to the bilateral hippocampus and the parahippocampal cortex, has no RSN or VBM changes and DTI revealed a trend towards reduced fornix FA. Contrary to our predictions, these results indicate that neither amnesic individual has obvious functional connectivity disruptions between brain areas, nor macro or microstructural white matter atrophy outside the MTL.

4.4.1. Rs-fMRI findings

Rs-fMRI neuroimaging of patient MTL3 revealed a significantly reduced connectivity of a number of brain regions within the PHN, including the parahippocampal cortex, posterior hippocampus and thalamus in the right hemisphere. In addition, there was significantly reduced co-activation between the PHN and areas beyond this network, such as the right insular cortex, planum temporale, middle temporal gyrus and inferior lateral occipital cortex, and the bilateral anterior and posterior cingulate gyri in comparison to controls. It is likely that the disruption to regions within and outside of the PHN reflect the relatively large brain lesion

in this patient encompassing the MTL structures in both hemispheres (including the amygdala, hippocampus, perirhinal cortex, entorhinal cortex, and parahippocampal cortex), and the temporopolar cortex, anterior fusiform gyrus, and anterior lateral temporal cortex in the right hemisphere (see Lee & Rudebeck, 2010a). As this is only the second study to identify the PHN through ICA and dual-regression analyses (Trachtenberg et al., 2011) the functional role of this RSN is yet to be clarified. However, the distinction between the anterior and posterior MTL regions is well documented, with the posterior portions of the hippocampus and the parahippocampal cortex being specifically implicated in the long term encoding of spatial representation (Epstein, 2008; Köhler et al., 2002; Maguire et al., 2003; O'Keefe & Nadel, 1978) and processing complex spatial information (Köhler et al., 2002; Lee & Rudebeck, 2010a; Lee et al., 2008). Patient MTL3 has exceptional low performance on neuropsychological tests of topographical recognition and her poor performance on complex spatial discrimination tasks that do not place an explicit demand on long-term mnemonic ability, have previously been well documented (Lee, Buckley, et al., 2005). It is, therefore, not implausible to suggest that this decrease in co-activation in the PHN may, to some degree, contribute to the cognitive deficits that have been observed in patient MTL3. Further investigations would be needed to verify this suggestion and will be discussed in Section 4.4.4.

Perhaps surprisingly, no significant differences in RSNs incorporating the hippocampus (e.g. PHN, DMN) were found in patient HC3 compared to controls, despite the presence of a significant hippocampal lesion in this patient. What is more, despite damage to a number of MTL structures, patient MTL3 also failed to show any significant reduction in the co-activation of the DMN in comparison to controls. This is in contrast to previous extensive research showing that patients suffering from mTLE or AD, conditions associated with extensive hippocampal and MTL pathology, have reductions in DMN connectivity in comparison to controls (Bai et al., 2008; Greicius et al., 2003; Z. Zhang et al., 2010). In addition to this, no changes were found in patients MTL3 or HC3 in relation to regions within frontal RSNs, such as the ECN, lFPN and rFPN, despite the evidence that co-activations within these regions in mTLE

and AD are altered and associated with neuropsychological performance (Agosta et al., 2012; Supekar et al., 2008; Wang et al., 2006; Z. Zhang, Lu, Zhong, Tan, Yang, et al., 2009; Zhou et al., 2010). There are two possible explanations for these discrepancies in findings between the current study and the existing mTLE/AD literature. First, the current single case approach and resulting reduced statistical power may have made subtle changes in resting functional connectivity difficult to detect (see section 4.4.4 for further discussion). Second, organic amnesia after insult to the MTL is not typically associated with attention or executive functioning deficits (Milner, 1972, 2005; Squire, 1980; Squire & Slater, 1978), that are seen in AD and mTLE (e.g. Allegri et al., 1999; Grady et al., 1988; Perry & Hodges, 1999). It may not, therefore, be surprising that no changes in frontal RSNs were seen.

4.4.2. White matter VBM findings

White matter VBM was conducted at the whole brain level to investigate possible macrostructure white matter changes within MTL3 and HC3 brains. Patient MTL3 showed a trend towards gross white matter reduction in the bilateral MTL regions and temporal poles, fornix, UF and right thalamus (Figure 4-5), whilst patient HC3 had no significant differences in gross white matter in contrast to controls. Although only a trend was observed in patient MTL3, this finding does not disagree with a previous investigation of 5 individuals with hypoxic amnesia and bilateral hippocampi lesions, which found macrostructure white matter reductions in the fornix, cingulum and bilateral UF using white matter VBM (Di Paola et al., 2011). Bearing in mind the use of uncorrected statistical thresholds in previous research to reveal hippocampal atrophy, as measured by VBM, in a single amnesic case (Cipolotti et al., 2006), it is highly possible that with an increase in patient numbers and thus, statistical power, similar significant findings to those of Di Paola et al. (2011) could be observed.

4.4.3. DTI findings

To investigate any potential differences in white matter microstructural integrity, we used a voxel-based approach (i.e. TBSS) first at the whole brain level, followed by the use of ROI. The

former allowed us to carry out an exploratory analysis across the entire brain without delineating individual regions and this revealed no obvious differences in either patients compared to controls. A more sensitive ROI approach, however, yielded significantly decreased FA in patient MTL3 in the body of the fornix and the right UF. These significant TBSS ROI results were further validated by probabilistic tractography of the right UF and fornix with mean FA extraction, with significantly decreased FA in both tracts in patient MTL3 compared to controls. Patient HC3 TBSS and probabilistic tractography results only showed a trend towards significantly reduced FA in the tail and body of fornix in contrast to controls.

Previous TBSS investigations into individuals with damage constrained primarily to the MTL and hippocampus (for example, mTLE and MCI) like patients MTL3 and HC3, also fail to show fiber tract changes at the whole brain TBSS level (Nguyen et al., 2011; O'Dwyer et al., 2011) and, similar to the present study, required the use of ROIs before a reduction in FA was observed (Nguyen et al., 2011). Our investigation, therefore, adds to the body of research that focal lesions within the MTL lead to subtle changes in white matter tracts that are only detectable after applying ROI analyses (Nguyen et al., 2011). Although tractography has previously revealed fornix and right and left UF FA reductions after MTL damage (Concha et al., 2009, 2005; Voets et al., 2009) no prior investigation has used our methodology to show the convergence of findings between TBSS and probabilistic tractography with mean FA extraction. By replicating our DTI findings using another analysis technique we can be confident that our results are not effected by partial volume errors associated with TBSS in regions of low FA (like the fornix) and accurately represent the changes in fornix and UF integrity in two MTL lesion individuals in comparison to age and education matched controls.

Although organic anterograde amnesia is most commonly associated with bilateral MTL damage, in particular to the hippocampi, previous investigators have suggested that the entire memory-limbic network, including the tracts of the Papez circuit (fornix, mammilo-thalmic tract and cingulum) and the UF may be compromised in individuals with long-term episodic memory deficits (Diehl et al., 2008; D. Gaffan & Gaffan, 1991; E. A. Gaffan et al., 1991; Nestor

et al., 2008). Our current findings in patient MTL3 support this notion, as changes were found in the major white matter outputs of the hippocampus and the temporal lobes, the fornix and right UF. The mechanism by which this white matter damage occurred is unknown and likely to be multifaceted. One possibility considering the extensive cortical damage to the hippocampi and right temporal lobe in patient MTL3, is Wallerian degeneration - the degeneration process that occurs to the axonal stump distal to a damaged axon (Waller, 1850). It is plausible that Wallerian degeneration occurred to the fornix and right UF after the death of the neurons within cortical regions where their respective perikarya are located, in particular the hippocampal pyramidal CA1 layer and the ventro-medial and polar temporal lobe (Coleman & Freeman, 2010). On the other hand, white and grey matter damage could have occurred at the original time of brain injury in patient MTL3 (in this case, viral encephalitis) due to reduced blood supply, neurotoxicity and/or altered metabolism. Given the relatively smaller hippocampal lesion in Patient HC3 it is perhaps not surprising that the TBSS and tractography analyses only suggest a trend towards reduced FA within the fornix.

4.4.4. General methodological issues and future directions

As stated previously, one limitation of the current study was the single case approach and consequently, reduced statistical power. To diminish the possibility of making a type 2 error, our statistical thresholds were adjusted accordingly when analysing the patients' RSN data and we created ROIs of tracts of interest in the DTI TBSS analyses. One cannot, however, rule out the possibility that following focal brain damage there are slight changes to RSNs and the macro and microstructure of the white matter, which can only be detected reliably when larger groups of patients are contrasted to controls. There were a couple of practical reasons why a limited number of amnesic patients underwent neuroimaging. Firstly, organic amnesia is a very rare condition and those patients with selective damage or relatively circumscribed lesions to the MTL are even fewer. Secondly, it is not uncommon for amnesic patients to be unsuitable for MRI investigation, for instance due to severe anxiety, claustrophobia, a previous history of epileptic fits, the presence of ferrous material in the body, or the use of

neuropsychopharmalogical medicine (e.g. for epilepsy, depression, etc). Indeed, neuroimaging and also behavioural studies of MTL lesion amnesiacs often adopt a single-case approach (e.g. Aggleton, Vann, Denby, et al., 2005; Bird et al., 2008; Maguire et al., 2001; Rosenbaum et al., 2007). Finding a way to significantly increase patient numbers in future studies of brain connectivity in MTL-damaged amnesic patients is an important challenge for the future. One potential solution is to conduct multi-research centre investigations incorporating patients across a number of regions, which would improve statistical power, increase sensitivity, and allow the findings to have greater generalization. This would help us decipher with greater confidence the intact and damaged functional and white matter connections following MTL damage, which may, in turn, lead to insights into regions in which plasticity could occur and, therefore, be targeted in rehabilitation. For example, based on the current findings that suggest preserved RSN and white matter integrity within the frontal lobes in MTL and HC3, rehabilitation protocols which rely on intact executive functioning, such as the goal-planning approach or reminder technological aids may be utlised (Wilson, 2008). Furthermore, experimental white matter training protocols, such as Cogmed (http://www.cogmed.com), that may stimulate the intact frontal lobes and possibly the reminder of the MTL could also be utilized in these patients.

Although ICA and dual-regression of the control group's Rs-fMRI scans revealed 8 separate components, none of these were identified as the AHN, a RSN that encompasses anterior regions of the MTL (Trachtenberg et al., 2011). As both patients have pathological damage to regions within the AHN this RSN would have been particularly interesting to investigate. ICA of Rs-fMRI is, however, data driven and thus, there is no investigator control over the sets of time-courses and associated spatial maps (components) found (Beckmann et al., 2005). As the current study is only, to our knowledge, the second investigation to find the PHN after ICA of Rs-fMRI data (Trachtenberg et al., 2011), future investigations are needed to replicate its existence using different Rs-fMRI analysis techniques and explore its possible functionality. For example, to achieve the latter, a future neuroimaging investigation could use

both Rs-fMRI and task-based fMRI to scan a group of MTL lesion amnesic patients and controls. During the task-based fMRI scan the participants could be asked to perform a task that activates the brain regions within the PHN, for example a spatial working memory paradigm (Lee & Rudebeck, 2010a) or an LTM encoding task (Filippini et al., 2009). One prediction is that amnesic patients may have reduced task based activity in the posterior hippocampus and parahippocampal cortex and that this may be related to similarly decreased co-activation in regions of their PHN. By using a larger patient group, correlational analyses could also be conducted between the MTL lesion patients' psychometric and experimental memory scores, and the mean connectivity of regions within the PHN.

Although extensive care was taken to ensure that our DTI results were verified using 2 complementary methodologies, TBSS is only sensitive to local changes in white matter integrity and does not provide direct insight into subtle changes in long-range connectivity (Smith et al., 2006). To be able to interrogate the long-range connectivity of the fiber tracts of MTL3 and HC3 in comparison to controls, we would need to carry out tractography-based connectivity analyses across the major fiber tracts of the brain. However, carrying out probabilistic tractography in both patients and all 32 controls by creating seed, waypoint and termination masks for the 9 major fiber tracts of the brain (i.e corpus callosum, fornix, UF, cingulum, angular bundle, cerebral peduncular projections to superior frontal lobes, Inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and arcuate fasciculus) would be significantly time demanding. If this significant practical issue can be overcome, future tractography analyses may provide additional information and detect small changes that our current methods are insensitive to, although by nature of being selective to individual tracts, they have the disadvantage of not being as regionally comprehensive as the TBSS approach adopted here.

A final additional factor that deserves consideration and further investigation is the possibility of brain recovery over time following the occurrence of non-progressive brain damage (e.g. as seen in stroke, Dijkhuizen et al., 2012). Both patients HC3 (1991) and MTL3 (1993) first presented almost 20 years prior to the current study, and particularly in the case of

a smaller focal lesion in patient HC3, there may have been significant changes in functional brain connectivity from the time the lesion occurred to the present day. This may explain, at least in part, why no significant changes to RSNs and white matter were observed in patient HC3. Previous DTI longitudinal investigations of traumatic brain injured individuals showed through comparison of scans at 8 weeks to 1 year that FA levels increased in some individuals and that this change in FA was associated with improved psychometric outcomes (Sidaros et al., 2008). Along these lines, a Rs-fMRI, DTI and psychometric investigation of individuals with MTL damage at 8 weeks, 1 year and 3 years following insult could be carried out in the future. The results of such a study would allow us to elucidate if there is a functional link between RSNs or white matter integrity and neuropsychological outcome. For example, it might be predicted that in individuals who demonstrate some recovery of LTM memory function, there may be increases in MTL-related RSN connectivity (e.g. DMN, PHN, AHN), as well as increases in FA in tracts connected to the MTL.

Chapter 5 - A potential spatial working memory training task to improve both episodic long-term memory and fluid intelligence

5.1. Introduction

One of the main questions raised from the experiments in Chapters 2 and 3 is whether the inherent existence of increased fornix microstructure in certain individuals underlies improved recollection memory, or whether it is the utilization and improvement of recollection in individuals over time that leads to an enhancement in fornix microstructure. As suggested previously, one means of investigating this issue is the use of extensive long-term episodic memory (EM) training in conjunction with DTI. The logic of this approach is that if EM can be reliably improved over time, then DTI can be used to determine whether improvements in EM performance are associated with increases in FA in specific white matter tracts such as the fornix. A number of previous investigations have shown that extensive cognitive and motor training is associated with brain plasticity in both the grey and white matter (Maguire et al., 2000; Maguire, Woollett, & Spiers, 2006; Scholz et al., 2009; Takeuchi et al., 2010). For example, Maguire and colleagues (Maguire et al., 2000; Maguire, Woollett, et al., 2006) showed that taxi drivers who had undergone 2-4 years of spatial memory training to acquire "The knowledge" of London streets had increased volume of the posterior hippocampi but decreased volume of the anterior hippocampi. What is more, number of years of navigation experienced correlated with hippocampal grey matter volume of the posterior hippocampi. Notably, however, despite an increasing amount of research (Morrison & Chein, 2011;

Ranganath, Flegal, & Kelly, 2011) there is currently no consensus as to what constitutes an effective EM training regimen. The current study, therefore, aimed to establish an EM training behavioural paradigm that could potentially be used in conjunction with DTI.

Over the past two decades EM training research has investigated the efficacy of memory training in young adults, older adults and in clinical populations using a wide range of approaches and protocols (Klingberg, 2010; Morrison & Chein, 2011; Rebok, Carlson, & Langbaum, 2007). The two most prevalent types of training protocols that have been investigated are EM strategy training and working memory (WM) training.

Mnemonic strategy training typically teaches individuals systems for remembering information, for example making up a story with items, grouping items into chunks or using mental imagery to make items more salient (Morrison & Chein, 2011; Rebok et al., 2007). These techniques robustly improve the performance on the trained task in both young and old adults (Ball et al., 2002; Carretti, Borella, & De Beni, 2007; Jobe et al., 2001; McNamara & Scott, 2001) and in patient populations (Cicerone et al., 2011; Hampstead et al., 2012). One of the main purposes of memory training, however, is to achieve effects not only in the trained task but also in non-trained cognitive tasks (i.e. for transfer to take place). Very few mnemonic strategy training studies have assessed if transfer occurs (Morrison & Chein, 2011), and most that have suggest that memory strategy training is highly specific (Ball et al., 2002; Jobe et al., 2001; Rebok et al., 2007). Counter to this, self-report measures suggest that individuals who undertake strategy memory training believe that there is a wider improvement in their everyday memory (Cavallini, Pagnin, & Vecchi, 2002; Willis et al., 2006).

Tasks ultilizing WM, the temporary retention and manipulation of information (Andrade, 2001; Atkinson & Shiffrin, 1968; Baddeley, 2003; Baddeley & Hitch, 1974; Conway, Jarrold, Kane, Miyake, & Towse, 2007; Miyake & Shah, 1999) have been widely used in cognitive stimulation packages and are somewhat successful in transfer to non-trained tasks, such as fluid intelligence (G*f*), cognitive control and reading comprehension (Chein & Morrison,

2010; Jaeggi, Buschkuehl, Jonides, & Perrig, 2008; Jaeggi, Buschkuehl, Jonides, & Shah, 2011; Klingberg et al., 2005; Olesen, Westerberg, & Klingberg, 2004; Westerberg et al., 2007). Most notably, Jaeggi and colleagues (2008) recently trained separate groups of healthy young adults in a 20 minute adaptive dual N-back task for 12, 15, 17, 18 and 20 days. They found that participants who trained for over 17 days improved significantly on an untrained G*f* task, the Bochumer Matrices-Test (BOMAT) (Hossiep, Turck, & Hasella, 1999) after training (i.e. the trained improvement in WM transferred to a different but associated cognitive construct).

Only a handful of the studies have investigated if WM training leads to successful transfer to untrained EM performance. Buschkuel and colleagues (2008) trained healthy 80 year old subjects on 3 visual WM span tasks consisting of coloured blocks and pictures of animals for 8 minutes, 2 times a week for 3 months (Buschkuehl et al., 2008). At immediate follow up in comparison to a physical activity control group, WM training led to improvements on a non-trained spatial WM task and a visual free-recall EM test (Buschkuehl et al., 2008). In addition, an ambitious study by Schmiedek and colleagues (2010), trained young and old healthy adults for 100 days on 6 tasks of perceptual speed, (3 comparison tasks, 3 choice reaction tasks), 3 tests of WM (alpha span, memory updating and spatial 3-back) and 3 tests of EM (word lists, number-noun pairs and object position memory). In young adults they found some positive transfer to untrained tasks of EM from the Berlin Intelligence Structure test (Jäger, Süß, & Beauducel, 1997) and in a word pairs test for the older adults (Schmiedek et al., 2010). The brevity of the tasks included in this cognitive training battery, however, make it difficult to ascertain which training components were critical for this EM improvement. What is more, extensive batteries of cognitive training tests can be time consuming and challenging to learn especially for patient populations.

Despite these positive findings, a number of studies have failed to find any EM performance benefit following WM training. In one ambitious study, 11,430 adults were trained in tests of planning, short-term memory, problem solving and maths and showed no specific improvement in transfer tests in comparison to an active control group, which included

an paired associates test (PAL) (Owen et al., 2010). It should be noted, however, that although this study excelled in terms of sample size, the findings should be interpreted with some caution as the amount of training participants were required to do was not controlled. Indeed, some training participants only carried out 2 training sessions, amounting to 20 minutes in total. More convincing evidence comes from Dahlin et al., (Dahlin, Nyberg, Bäckman, & Neely, 2008) who showed that 5 weeks of training on WM tasks in both young and old adults did not lead to improvement on a paired associates test or a concrete nouns recall task (Dahlin, Nyberg, et al., 2008). It is worth noting that neither of the above WM training studies were specifically designed to tap the cognitive processes or neural correlates underlying EM. This is important as investigators (Jonides, 2004; Olesen et al., 2004) have hypothesised that for successful transfer to occur the trained and transfer tasks must engage overlapping cognitive processes and neural mechanisms. Support for this theory comes from an fMRI training study that found that 5 weeks of WM updating training lead to successful transfer to a non-trained N-back task and that this was mediated by activity in the striatum on both tasks (Dahlin, Neely, et al., 2008).

Traditionally, WM and EM have been conceptualized as cognitively and neurally distinct constructs (Baddeley, 2000; Baddeley & Warrington, 1970; Craik, 2012; Craik & Lockhart, 1972; Shallice & Warrington, 1970). This 'multi-store' theory of memory was primarily based on neuropsychological investigations of MTL lesion patients who exhibited EM deficits but intact WM (Baddeley & Warrington, 1970; Scoville & Milner, 1957; Squire, Knowlton, & Musen, 1993) and frontal lobe lesion patients who conversely appeared to have WM deficits but spared EM (Baddeley & Warrington, 1970; Shallice & Warrington, 1970; Warrington & Shallice, 1969). This apparent double dissociation was further supported by neuroimaging and single unit recording that showed WM processes were primarily subserved by the lateral prefrontal cortices (Courtney, Ungerleider, Keil, & Haxby, 1997; D'Esposito, Postle, Ballard, & Lease, 1999; Petrides, Alivisatos, Meyer, & Evans, 1993; Postle, Berger, & D'Esposito, 1999), whereas the MTL, and specifically the hippocampus, were predominantly involved in the

encoding and retrieval of long-term memories (Daselaar et al., 2001; Dolan & Fletcher, 1999; Otten, Henson, & Rugg, 2001; Wagner et al., 1998). These findings led to the classical idea that the MTL primarily supports EM or declarative memory (Squire, 1986; Squire et al., 2004), whilst the lateral PFC, is involved in the maintenance, manipulation and monitoring of information needed for successful WM (Fletcher & Henson, 2001; E. E. Smith & Jonides, 1999).

Although the traditional view of a neuronal and cognitive dissociation between WM and EM is still prevalent, recent evidence has questioned its validity (see also Chapter 1). For example, although individuals with MTL lesions do not exhibit WM deficits when the stimuli to be remembered are verbal, such as words (Baddeley & Warrington, 1970) or numbers (Cave & Squire, 1992), they do have issues retaining novel visual objects (Holdstock, Gutnikov, Gaffan, & Mayes, 2000; Holdstock et al., 1995; Owen et al., 1995) faces (Ezzyat & Olson, 2008; E. A. Nichols et al., 2006; Olson, Moore, et al., 2006), spatial information (Olson, Moore, et al., 2006) and relational and topographical information (Hannula et al., 2006; Hartley et al., 2007; Olson, Page, et al., 2006) over a few seconds. Crucially, neuroimaging investigations also show parahippocampal, entorhinal, perirhinal and hippocampal activity during WM paradigms using faces (Ranganath & Esposito, 2001), scenes (Lee & Rudebeck, 2010a; Stern et al., 2001) and novel objects (Davachi & Goldman-Rakic, 2001; Ranganath et al., 2005). Moreover, the degree of MTL activity during the maintenance of items in WM has been suggested to be predictive of subsequent EM success for the same items (Ranganath et al., 2005) .

Two meta-analyses by D'Esposito and colleagues of a number of lateral PFC lesion studies showed that these lesions do not necessarily lead to deficits in WM span tasks (D'Esposito, Cooney, Gazzaley, Gibbs, & Postle, 2006; D'Esposito et al., 1999), whilst problems with initiating strategies spontaneously to encode information can lead PFC damaged individuals to exhibit impaired EM performance (Gershberg & Shimamura, 1995). Indeed, functional neuroimaging studies show that PFC regions are active during EM in particular when a complex action (e.g. a semantic decision about the stimuli) must be performed by the participants during encoding or retrieval (Dobbins et al., 2002; Fletcher & Henson, 2001).

Furthermore, computational models indicate there is a dynamic interaction between WM and EM, where the ability to maintain information in WM is crucial to EM encoding and retrieval (Burgess & Hitch, 2005). Taking these findings into consideration, recent arguments against the neural distinction between WM and EM have been made (Ranganath & Blumenfeld, 2005; see, however, Jeneson and Squire, 2012 for a recent rebuttal of this view) with a number of unitary store models proposing that EM and WM are not supported by separable neuronal regions, but by the same neocortical memory network that can either be reactivated in response to external stimuli or top-down signals for memory retrieval (Fuster, 1997; Nairne, 2002).

Further evidence that the same neural correlates may subserve both WM and EM comes from studies that have demonstrated that the MTL does not subserve declarative memory exclusively, but may also be critical for higher order perceptual processes (Buckley et al., 2001; Bussey et al., 2002; Murray et al., 1999; Graham et al., 2010; Baxter, 2009). According to this work, the perirhinal cortex processes complex conjunctions of object features whereas the hippocampus subserves complex spatial representations (Buckley & Gaffan, 2006; Bussey et al., 2005; D. Gaffan, 2002; Murray et al., 2007). For example, patients with bilateral hippocampal damage exhibit deficits on complex scene discrimination tasks, while cases with perirhinal cortex damage demonstrate problems in the discrimination of complex objects (Lee, Bussey, et al., 2005; Lee, Buckley, et al., 2005, 2006). Convergent evidence comes from fMRI work in neurologically healthy individuals, which has found increased posterior hippocampal and parahippocampal activity during scene discrimination judgments and perirhinal cortex activity during face discrimination (Lee et al., 2008). These findings have led to the suggestion that the functions of the MTL are better understood in terms of the types of information that they represent, rather than the cognitive processes they mediate (Graham et al., 2010; Saksida & Bussey, 2010). Thus, in the case of the hippocampus, for example, a disruption to complex spatial representations following hippocampal damage may lead to deficits in EM, WM, and/or higher-order perception if a demand is placed on complex spatial processing (Bird & Burgess, 2008b; D. Gaffan, 2002; Graham et al., 2010; Lee, Barense, et al., 2005). Indeed, a number of

studies have found that individuals with bilateral hippocampal damage show impairments on EM recognition memory tests of topographic scenes but not faces or objects (Bird et al., 2007, 2008; Cipolotti et al., 2006; Taylor et al., 2007).

In the light of the discussion above, the current study aimed to create a WM training task that would enable successful transfer to other cognitive domains, in particular episodic memory. To this end, we adapted a dual N-back WM task that was previously associated with successful transfer to G*f* (Jaeggi et al., 2008, 2011), and was designed to (1) minimise strategizing opportunities, and (2) adapt in a graded fashion to the participant performance, two factors that effect the likelihood of transfer (Buschkuehl & Jaeggi, 2010; Ranganath et al., 2011). To place an emphasis on MTL regions in particular the hippocampus, we emphasised spatial processing by asking participants to look into a 3D room with 8 picture frames in it. Within these picture frames, pictures of scenes were presented and participants were asked to monitor both the scene images *and* the locations in which they were presented (see Figure 5-1 and Methods section for full explanation). Given previous findings (Jaeggi et al., 2008, 2011) and the modifications we made to the dual N-back WM task reported in this study, we predicted that sustained training on our task would lead to improved (1) G*f* as measured by the BOMAT; (2) episodic memory as measured by a scene and object recognition receiver operating characteristic (ROC) memory tasks, (3) spatial WM as measured by spatial span and performance on the training task; and finally (4) spatial perception as measured by a complex spatial discrimination task (Lee et al., 2005).

It is important to highlight that, in contrast to many previous cognitive training studies, we assessed cognitive performance using a range of experimental tasks (for full details see Methods). Prior research has primarily used psychometric neuropsychological tests to investigate transfer to various cognitive constructs of interest (Chein & Morrison, 2010; Dahlin, Nyberg, et al., 2008; Jaeggi et al., 2008, 2011; Olesen et al., 2004) and although these tests are fast to administer and reliable, they are not necessarily sufficiently sensitive to detect small changes in cognitive performance following training (Ranganath et al., 2011). In addition to

this, many standard neuropsychological tasks have not been designed to measure or target specific cognitive processes, for example recollection (i.e. remembering accompanied by the recall of contextual information) and familiarity (i.e. feeling of knowing) in the domain of episodic memory.

5.2. Methods

5.2.1. Participants

56 neurologically healthy right-handed young volunteers who were not on any psychoactive medication were recruited from the Oxfordshire area to take part in this study, with half of these forming the training group, and the other half acting as a control group. One training participant was excluded from our analyses due to illness that interfered with training and the second assessment session. For the remaining participants, there were no significant differences (all $p > 0.4$) between the training group and controls in terms of age, years of education, verbal IQ as measured by the National Adult Reading test (NART) (Nelson, 1982) or depression as measured by the Beck Depression Inventory-II (Beck, Steer, & Brown, 1996) (Table 5-1).

Table 5-1: The demographic details of the training and control participants.

	Trainers Mean (S.D.)	**Controls** Mean (S.D.)
Female/Male (N)	13/14	14/14
Age	25.36 (4.45)	25.49 (4.68)
Years of Education	16.62 (2.87)	16.14 (2.51)
BDI	2.89 (3.29)	3.18 (3.85)
NART	36.33 (8.96)	37 (7.94)

5.2.2. Behavioural Tests

5.2.2.1. Procedure

Participants in the training group received a copy of the training task on their personal laptop computers and were instructed to train on the task in their own time for 20 minutes a day, 5 days a week for 4 weeks. A performance log file was automatically generated after each training session and the participants were required to supply this to the investigators. Each participant's progress was updated daily on a web based performance spreadsheet. A pre-training assessment session took place the day before training began and the post-training session no more than 2 days after training was completed. The control group completed the same pretest and posttest evaluation sessions as the trainers 28 days apart; however, they did not undertake any cognitive training during this time.

5.2.2.2. Assessment sessions

During the pre-test and post-test sessions all participants completed a battery of cognitive tests; the scene N-back training task, the BOMAT (Hossiep et al., 1999), scene and object recognition ROC memory tests, spatial span and the scene oddity paradigm. Other than the BOMAT which was administered on paper, all the other tasks were administered on a 15" laptop computer. Different versions of each task were presented across the two assessment sessions, and within each session, the same tasks were administered in the same order across all participants.

5.2.2.3. Dual N-back Training task

The training task was a dual N-back spatial working memory task developed by the authors using Presentation (Neurobehavioural Systems, Inc). In this task, participants were presented with a 3-dimensional virtual reality room that contained 8 picture frames (Figure 5-1). Images of real-world scenes were presented one at a time in the picture frames (stimulus duration , 1000ms, interstimulus interval 250ms) and participants were asked to keep track of the real-world scenes as well as the locations in which they were presented. The task started as a 1-

back task on the first block of training in the first training session, and was ratcheted to N-back in subsequent blocks according to the participant's performance. An 'S' key response was required when a scene image was repeated (2 successive identical scenes in the case of 1-back; 2 identical scenes separated by a different image in the case of 2-back, and so forth) and a 'L' when a picture frame location was repeated (2 scenes presented successively in the same location in the case of 1-back; 2 scenes presented in the same location across 3 trials in 2-back, and so forth; see Figure 5-1 for schematic of task). Each training session comprised of 12 blocks, presented one after another. 30 scenes were presented in each block and of these 6 were scene targets, 6 were location targets and 2 were both scene and location targets. If the participant made fewer than 3 errors in both scene and location modalities within a block, the level of N increased by one in the next block. If more than 5 errors were made the level of N was decreased by 1 (minimum 1-back) and in all other cases the level of N remained the same.

The scene images comprised of a set of 440 unfamiliar indoor and outdoor grayscale photographs of scenes, which did not contain people, objects, or words. These scenes were specifically picked so that they could not be easily encoded verbally. The N-back training task was quasi randomized so that in each training session a scene was only selected once by the programme.

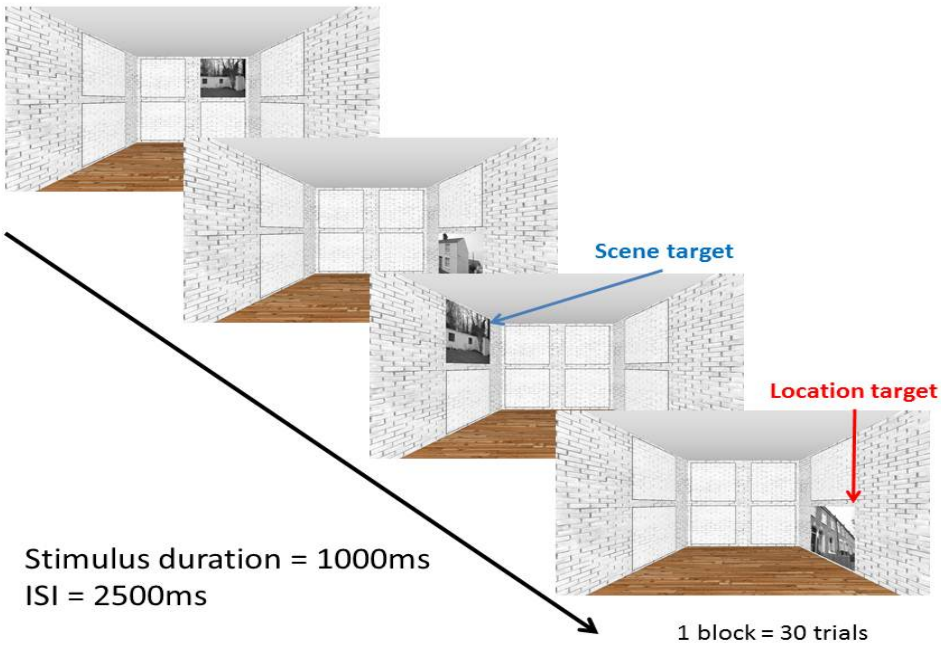

Figure 5-1: Schematic diagram of training paradigm. In this example, participants had to detect spatial locations and scene images that were identical to those presented two trials earlier (2-back task). The N-back requirement started at 1 and varied with performance across training.

5.2.2.4. Bochumer Matrices-Test (BOMAT)-advanced-short version

The BOMAT is a non-verbal neuropsychological test of G*f* (Hossiep et al., 1999). In each trial a 5 x 3 matrix of patterns is presented to the participant with one empty field in the matrix. The participant must then decide which pattern (out of 6 options) completes the matrix. In the advanced short version, there are 29 matrices for the participant to complete, one after another. Due to time restrictions and to reduce the possibility of ceiling effects associated with some tests of G*f*, participants were given 10 minutes to complete as many patterns as they could in each assessment session (see Jaeggi et al., 2008 for a similar procedure). The number of correct responses during this time served as a measure of G*f* for each participant. Version A of the BOMAT was presented in the pretest session and version B in the posttest session.

5.2.2.5. Recognition memory tasks

One scene and one object recognition task were administered in each assessment session. The procedure was identical across both sessions, although different stimuli were used. Each scene task involved 240 grayscale photographs of unfamiliar indoor and outdoor scenes, which did not contain people, objects, or words. These scenes were all different to those used in the N-back training task. For each object test, 240 grayscale photos of everyday objects were used. In both tests the stimuli were split into 120 items for an encoding phase and 120 foil items, which were presented with the encoding items for a test phase. In the encoding phase participants were presented with individual images and asked whether each scene was indoor or outdoor, or each object could fit in a shoebox. Following a twenty minute delay, during which an unrelated distracter task was completed, the test phase took place. Participants were presented with the encoding items intermixed randomly with the foils and asked to make a recognition judgment for each item using a 6-point confidence scale ("1" = confident an item is new; "6" = confident an item is old).

Receiver operating characteristic (ROC) curves were derived for each task by plotting P(hits) vs. P(false alarms) starting at the most confident response level (hits = P(6|old); false alarms = P(6|new)), and then cumulatively at subsequent confidence levels (hits = P(6|old) + P(5|old); false alarms = P(6|new) + P(5|new), etc). The dual process signal detection model (DPSD) (Yonelinas, 1994) was fit to this data, which assumes that recognition memory consists of independent recollection and familiarity components. A Microsoft Excel Solver that implements a sum of squares search algorithm was used to obtain estimates of recollection and familiarity for each participant. In addition, the d-prime score (z(P(hits) – z(P(false alarms)) was calculated as a general measure of performance.

5.2.2.6. Scene Oddity

The scene oddity test is an 'odd-one-out' paradigm that has been utilized extensively to investigate scene perception abilities in both clinical and healthy populations (Lee, Buckley, et

al., 2006; Lee et al., 2008). Two versions of the tasks were designed (one for each assessment session), and each consisted of 50 trials comprising of virtual reality scenes created using a computer game (Deus Ex, Ion Storm L.P., Austin, TX) and a freeware software editor (Deus Ex Software Development Kit v1112f). On each trial, 2 different views of the same scene were paired with another view of a different scene. The 'odd one out' scene was similar in appearance to its paired scene but there was a difference with respect to the placement or dimension of one or more features. Participants were given 8 seconds to identify the 'odd-one-out' and pressed the corresponding response key (1 = bottom right scene, 2 = top scene, 3 = bottom left scene) during a fixation cross presented immediately after each trial. The proportion of correct 'odd-one-out' judgments was used as the measure of performance.

5.2.2.7. Spatial span

This spatial span test is an adapted version of the classic Corsi spatial span task (Milner, 1971). Participants were asked to remember sequences of location that were illuminated on a 4 x 4 grid presented on a touch-sensitive screen. In each trial a sequence of red squares flashed blue for 500 ms with a 250 ms interval between each flashing square. Once the sequence was completed a short tone prompted the participant to touch the correct sequence of locations. 20 trials were presented in total, beginning with 4 sequences of locations to remember at the start of the test. The task difficulty adapted to the participants performance, with the sequence lengthened by 1 if the trial was completed correctly and decreased by 1 if completed incorrectly. A rule was programmed to ensure sequences were unstructured (Bor, Duncan, Wiseman, & Owen, 2003), that is, two successive locations were never in the same column, in the same row, or on the same diagonal. This was to ensure participant's performance was not aided by the ability to chunk squares into higher level patterns (Bor, Duncan, & Owen, 2001). The spatial span capacity for each participant was calculated as the average length of sequences undertaken in the twenty trials.

5.2.2.8. Data analyses

Analyses were conducted using IBM SPSS software. Two-tailed independent sample t-tests were first used to explore any differences between the trainers and control group. Previous investigations (Jaeggi et al., 2011) have indicated the quality of training that is, how much the trainers improved during their 20 days of N-back training, significantly affects the likelihood of transfer. To investigate this possibility our participants were median split into high gain (HG) and low gain (LG) groups based solely on their average N-back training gain and were compared to controls using one-way ANOVAs. Since only three means were involved (and thus, Family Wise Error rate = α), we used three 2-tailed linear contrasts (HG vs. LG, HG vs. controls, LG vs. controls) to explore these ANOVAs further (Howell, 2010). Given the unequal sample sizes following median-split of the trainers, we paid particular attention to homogeneity of variance between groups. When this was violated as indicated by the Levene statistic, the Welch procedure was used and subsequent linear contrasts were adjusted.

5.3. Results

Participants trained for 20 days on the spatial working memory task and their performance on the training task, the BOMAT and 2 recognition memory tests was compared to a group of matched non-trainers. To investigate any changes in performance, gain scores (post- minus pre-training score) were calculated for all tasks.

As expected, the training group possessed significantly greater gain scores on the training task compared to the control group ($t(53) = 7.59$; $p < 0.0001$). When the training group was further median split into a high gain (HG) group (n = 14) and a low gain (LG) group (n = 13), a one-way ANOVA revealed a significant effect of group (Welch F"$(2, 25.10) = 53.80$, $p < 0.0001$; Figure 5-2). There was a significant difference between the HG and LG groups ($t(15.85) = 5.67$, $p < 0.0001$), the HG group and controls ($t(15.30) = 8.83$, $p < 0.0001$), and the LG group and controls ($t(29.85) = 7.24$, $p < 0.0001$). The improvement in performance of both HG and LG groups over the 20 days of training could be explained by a linear function (HG: $R^2 = 0.97$, F(1,

18) = 253.05, p < 0.0001; LG: R^2 = 0.89, F(1, 18) = 68.59, p < 0.0001).

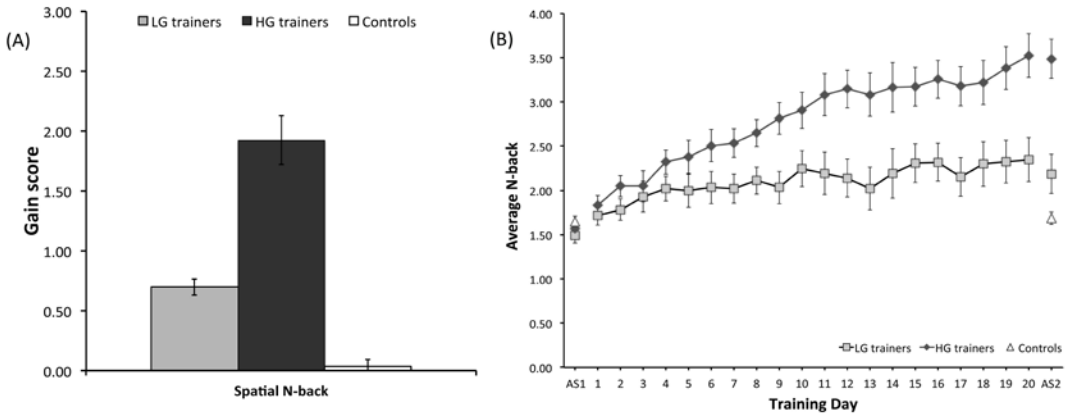

Figure 5-2: *(A) Mean gain scores (±S.E.) on the training task; (B) Change in performance across 20 days of training for the LG and HG groups. The mean scores at the first (AS1) and second (AS2) assessments are also shown.*

Supporting previous work (Jaeggi et al., 2008), training led to significant improvement on the BOMAT. When treated as a single group, the trainers made a significantly greater improvement on this test in comparison to controls (t(53) = 3.14, p = 0.003). A one-way ANOVA also revealed a significant effect of group when the trainers were median-split (F(2, 52) = 5.50, p = 0.007), with a significant difference between the LG group and controls (t(52) = 3.15, p = 0.003), as well as between the HG group and controls (t(52) = 2.00, p = 0.05). There was no significant difference between the HG and LG trainers (t(52) = 1.05, p = 0.3; Figure 5-3). A further 2-tailed t-test to investigate whether the greater numerical gain on the BOMAT in the LG group compared to the HG group may be explained, in part, by pre-existing individual differences revealed a trend towards the LG group posting a significantly lower BOMAT score compared to the HG group on the first assessment (t(25) = -1.84, p = 0.08; see Table 5-2 for each groups behavioural scores at the pre-and post-assessments).

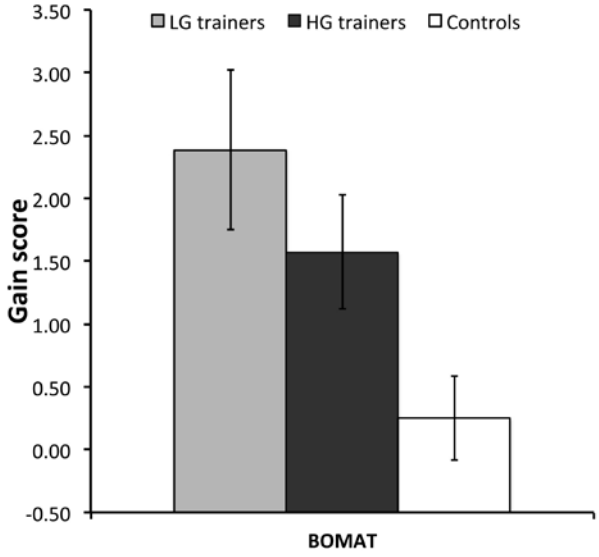

Figure 5-3: Mean gain scores (±S.E.) on the BOMAT for each participant group.

Our object and scene recognition tasks not only provided a general measure of EM (d'), but also allowed us to assess recollection and familiarity via receiver operating characteristic (ROC) analyses. To obtain an overall indication of episodic memory performance, we created recognition composite scores by averaging the d', recollection and familiarity gain scores across the two recognition tasks. Importantly, there was a significant positive correlation between the two recognition tests on all measures (d' gain: $r = 0.55$, $p < 0.0001$; recollection gain: $r = 0.61$, $p < 0.0001$; familiarity gain: $r = 0.34$, $p = 0.01$). Although some negative scores were observed due to the second assessment tasks being more difficult than those in the first session, this does not affect the interpretation of our findings as all participants received identical tests and it is the differences in gain scores between groups that is critical. We found no significant difference in gain on any of the composite scores between the trainers, when considered as a single group, and non-trainers (all $t(52) < 1.7$, $p \geq 0.1$). When HG and LG trainers were considered separately, however, striking differences emerged (Figure 5-4). There was a significant effect of group on all three composite scores (d': Welch F"$(2, 24.77) = 5.87$, $p = 0.008$, recollection and familiarity: both $F(2, 52) > 5.9$, $p \leq 0.005$), and for each composite score, there was a significant difference between the HG and control groups (d': $t(16.87) = 2.46$, $p = 0.03$; recollection and familiarity: both $t(52) > 3.0$, $p \leq 0.004$), and the HG and LG

groups (d': $t(18.97) = 3.40$, $p = 0.003$; recollection and familiarity both $t(52) > 2.9$, $p \leq 0.005$). There were no significant differences between the LG trainers and controls on any of the recognition composite scores (d': $t(26.18) = 1.86$, $p = 0.08$; recollection and familiarity: both $t(52) < 1.0$, $p \geq 0.3$). Notably, the HG and LG groups performed similarly in the first assessment session on all measures (all $t(25) < 1$, $p > 0.3$), suggesting that the difference in EM improvement between these groups following training cannot be attributed to any differences in their pre-training EM ability.

To explore the recognition data further, we considered the object and scene tasks separately. One-way ANOVAs revealed a significant effect of group on d' gain for both tasks (scene: Welch F"$(2, 27.07) = 3.55$, $p = 0.04$; object: $F(2, 52) > 10.30$, $p < 0.0001$), familiarity gain for both tasks (both $F(2, 52) > 3.2$, $p < 0.05$), and recollection gain for the object task ($F(2, 52) = 6.44$, $p = 0.003$), with a trend for recollection gain on the scene task ($F(2, 52) = 2.98$, $p = 0.060$). There was a significant difference between the HG group and controls on all three performance measures for the object recognition task (all $t(52) > 2.6$, $p \leq 0.01$), as well as a significant difference between the HG and LG trainers (all $t(52) > 2.9$, $p \leq 0.005$). On the scene task, there was a significant difference between the HG and LG groups on d' gain ($t(15.25) = 2.30$, $p = 0.04$), recollection gain and familiarity gain (both $t(52) > 2.1$, $p \leq 0.03$), a significant difference between the HG group and controls on recollection gain and familiarity gain (both $t(52) > 2.1$, $p < 0.04$), but not between the HG trainers and controls on d' gain ($t(16.79) = 1.45$, $p = 0.17$). On both scene and object tasks, there were no significant differences between the LG trainers and controls on any of the recognition measures (Scene d': $t(38.05) = 1.79$, $p = 0.08$; all others $t(52) < 1.3$, $p \geq 0.2$).

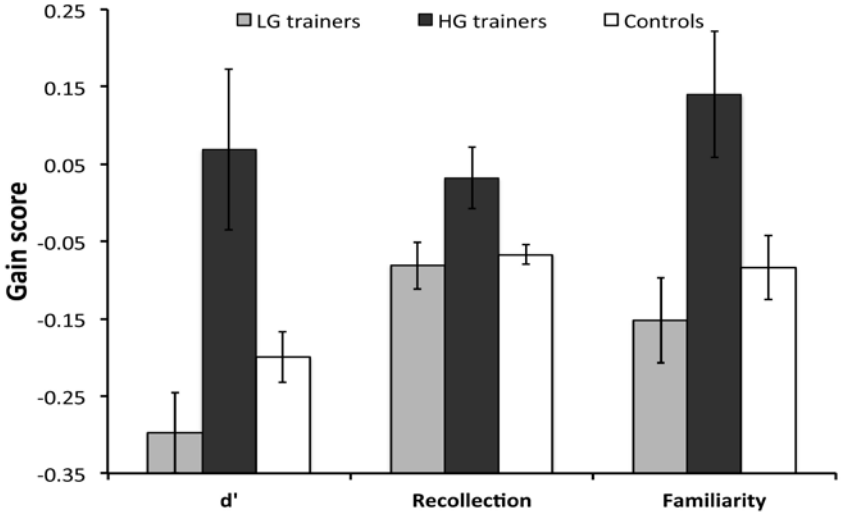

Figure 5-4: Mean gain scores (±S.E.) on the EM composite scores.

For the spatial span and oddity task gain there was no significant differences when the trainers were treated as one group in comparison to controls (both t(53) <0.5, p >0.7). Likewise, when trainers were split into HG and LG groups in contrast to controls, one-way ANOVA's showed there was no significant effect of group for the spatial span (Figure 5-5A) or scene oddity (Figure 5-5B; spatial span: Welch F"(2, 30.69) = 0.096, p = 0.91; oddity: F(2, 52) = 0.56, p = 0.57).

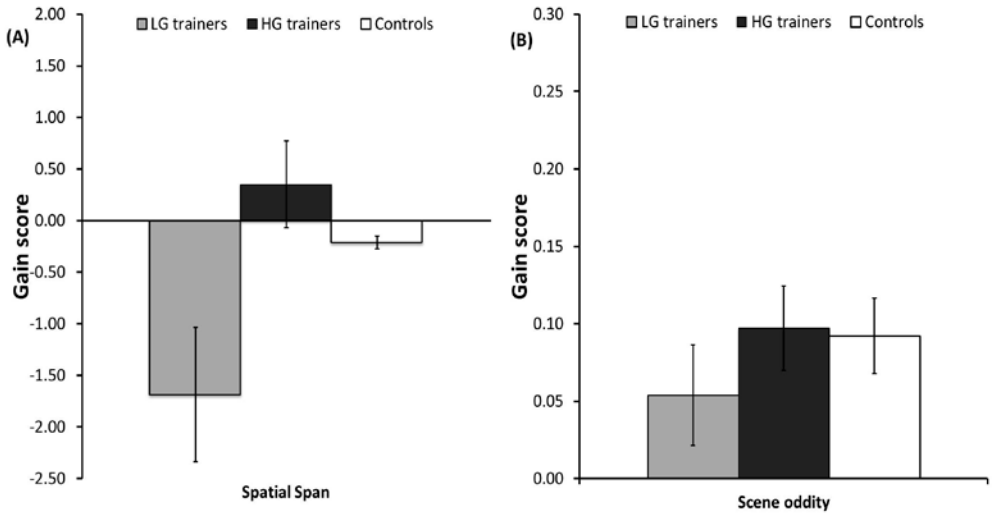

Figure 5-5: Mean gain scores (±S.E.) on the (A) Spatial Span task and (B) Scene Oddity task for the LG and HG trainers and controls.

Table 5-2: All average behavioural scores and standard deviation (S.D) for each participant group pre- and post-training.

	Session	LG Trainers	HG trainers	All trainers	Controls
Spatial N-back (S.D)	Pre-test	1.49 (0.27)	1.57 (0.31)	1.53(0.28)	1.65 (0.38)
	Post-test	2.19 (0.42)	3.49 (0.82)	0.28 (0.94)	1.69 (0.43)
BOMAT (S.D)	Pre-test	6.69 (2.29)	8.36 (2.41)	7.55 (2.41)	7.5 (2.36)
	Post-test	9.08 (1.89)	9.93 (2.13)	9.59 (1.99)	7.75 (2.53)
Object ROC recognition test - d'prime (S.D)	Pre-test	1.38 (0.33)	1.45(0.42)	1.42 (0.37)	1.25 (0.39)
	Post-test	1.02 (0.37)	1.54 (0.53)	1.29 (0.53)	1.01 (0.43)
Object ROC recognition test - recollection (S.D)	Pre-test	0.3 (0.15)	0.26 (0.16)	0.28 (0.15)	0.26 (0.14)
	Post-test	0.22 (0.14)	0.36 (0.16)	0.27 (0.16)	0.15 (0.12)
Object ROC recognition test - familiarity (S.D)	Pre-test	0.85 (0.55)	1.02 (0.38)	0.94 (0.47)	0.95 (0.4)
	Post-test	0.616 (0.61)	1.13 (0.48)	0.88 (0.6)	0.8 (0.38)
Scene ROC recognition test - d'prime (S.D)	Pre-test	1.13 (0.35)	1.17 (0.34)	1.15 (0.33)	1.14 (0.36)
	Post-test	0.9 (0.37)	1.28 (0.45)	1.1 (0.46)	1.03 (0.45)
Scene ROC recognition test - recollection (S.D)	Pre-test	0.25 (0.12)	0.22 (0.11)	0.23 (0.12)	0.21 (0.12)
	Post-test	0.16 (0.11)	0.22 (0.15)	0.19 (0.14)	0.14 (0.09)
Scene ROC recognition test familiarity (S.D)	Pre-test	0.69 (0.42)	0.79 (0.25)	0.74 (0.34)	0.79 (0.34)
	Post-test	0.62 (0.4)	1.01 (0.4)	0.99 (0.89)	0.79 (0.35)
Spatial Span (S.D)	Pre-test	5.84 (0.6)	5.81 (0.66)	5.83 (0.62)	5.82 (0.85)
	Post-test	6.05 (0.47)	6.06 (0.78)	6.06 (0.64)	5.98 (0.95)
Scene oddity (S.D)	Pre-test	0.55 (0.09)	0.57 (0.11)	0.56 (0.1)	0.52(0.11)
	Post-test	0.6 (0.12)	0.67 (0.11)	0.64 (0.12)	0.61 (0.1)

5.4. Discussion

To our knowledge this is the first investigation to demonstrate that an extensive cognitive ability training regime incorporating multiple tasks is not necessary to improve episodic memory (EM). Instead practice on only a single intensive, spatial working memory task can enhance EM when the quality of training, i.e. the level of training improvement achieved, is

taken into account. What is more, spatial working memory training lead to improvements in G*f* in all participants irrespective of their training improvement.

5.4.1. Transfer to EM

As predicated, this study showed that 20 days of training on a single WM task leads to improved performance on a scene and object recognition test in the HG trainers in comparison to the LG trainers and controls. This contrasts with previous investigations in which WM training transfer effects to EM have been weak or absent (Buschkuehl et al., 2008; Dahlin, Nyberg, et al., 2008; Owen et al., 2010). Moreover, to our knowledge, this is the first study to utilize a single WM training task and find it transfers successfully to EM. There are a number of theoretical reasons why one might expect WM training to benefit EM. Firstly, investigators have shown that PFC-dependent executive functions are critically involved in successful EM encoding and retrieval, especially when complex decisions concerning the retrieved information are required (Dobbins et al., 2002; Fletcher & Henson, 2001; Gershberg & Shimamura, 1995; Rajah & McIntosh, 2006). More specifically, WM processes may interact directly with EM, with the ability to maintain information in WM possibly having a significant impact on the encoding and retrieval of episodic memories (Bunting, Conway, & Heitz, 2004; Burgess & Hitch, 2005). Considering the hypothesized close interactions between WM and EM, it may not be surprising, therefore, that 20 days of practice on a WM executive task aided EM encoding and retrieval in the HG group. What is more, it has been suggested that the neural mechanisms underlying WM and EM may not be as distinct as previously thought. Traditionally, the MTL has been associated with EM but not WM, whereas the lateral PFC has been suggested to be critical for WM and not EM (Fletcher & Henson, 2001; E. E. Smith & Jonides, 1999; Squire et al., 2004). However, this view has recently been challenged (Ranganath & Blumenfeld, 2005), with recent researching showing that patients with MTL lesions exhibit significant deficits when WM tasks involve specific stimuli, such as faces (Ezzyat & Olson, 2008; E. A. Nichols et al., 2006; Olson, Moore, et al., 2006), novel objects (Holdstock et al., 1995; Owen et al., 1995) and stimuli placing a high demand on relational or spatial processing (i.e. topographical scenes) (Hannula

et al., 2006; Hartley et al., 2007; Olson, Page, et al., 2006). Crucially, comparable WM tasks have been associated with MTL involvement in functional neuroimaging studies (Hannula & Ranganath, 2008; Lee & Rudebeck, 2010a; Piekema, Kessels, Mars, Petersson, & Fernández, 2006), with stimulus novelty also being a critical factor (Ranganath & Esposito, 2001; Stern et al., 2001).

Having considered the overlapping neural correlates of WM and EM, we suggest the critical factor that led to successful transfer from WM to EM was the type of stimuli that were presented during training in the present study. The MTL is recruited during WM tasks when stimuli require complex spatial/relational processing (Hannula & Ranganath, 2008; Hartley et al., 2007; Lee & Rudebeck, 2010a). In an effort to target the MTL, our training task was designed to maximise spatial processing, and subjects were required to monitor 8 spatial locations within a 3D room and also a large collection of 440 unique spatial scenes (besides those used as repetitions, no image was used more than once in each training session). This is in stark contrast to previous WM training studies that have used relatively limited pools of 2D spatial location, colours, digits, letter or animal pictures, which leads to more frequent stimulus repetition throughout training.

In this study, the quality of training, that is how much participants improved during the 20 days of training, had a significant effect on transfer, with HG, and not the LG trainers demonstrating a significant improvement on both EM tasks. It appears, therefore, that a certain degree of WM training improvement is necessary before a successful transfer to EM is observed. A number of investigators have suggested that participant individual differences in training performance is important to evaluate in regard to transfer effects (Buschkuehl & Jaeggi, 2010; Jaeggi et al., 2011; Morrison & Chein, 2011; Ranganath et al., 2011). A recent study where children with an average age of 9.12 years trained on an adaptive single spatial N-back task for 4 weeks, showed that those who improved the most on the training task (i.e. those with training gain performance above the training group median) had significantly increased G*f* scores post training, in comparison to the controls and trainers whose training

gain performance was below the training group median (Jaeggi et al., 2011). The current investigation converges with this study by identifying inter-subject variability in training performance as a vital variable to monitor and account for in cognitive training research and analysis. In future investigations, it would be interesting to determine the source of the individual differences in training task improvement, for example if they occur due to differences in motivation, innate abilities, or both. What is more, the possibility that participants may benefit from personalised training regimes that are tailored to their individual abilities and motivations could also be explored.

It is worth highlighting that we used ROC recognition tasks incorporating confidence judgements to assess EM, which may be more sensitive than standard neuropsychological assessment of EM or basic recognition and free recall paradigms. We found that on the object recognition memory task all measures (d', recollection and familiarity) benefited from successful training, whereas on the scene recognition memory task, successful training was associated with significantly increased recollection and familiarity scores, with a trend towards significance for d'. Therefore, despite the accumulation of evidence indicating that different MTL structures may be important for distinct EM processes (Brown & Aggleton, 2001; Eichenbaum et al., 2007), or processing of different types of information (Murray et al., 2007), training on a spatial WM task appears to lead to an unspecific improvement in EM, irrespective of stimuli type. This would suggest transfer is not being mediated solely by regions of the MTL since if this were the case, we would have expected training related improvement only on tests presenting specific stimulus categories (i.e. scenes but not objects) or on specific EM processes (i.e. hippocampal-mediated recollection). Successful performance of our WM training task required high levels of attention, cognitive control, spatial processing and mnemonic abilities. Hence, it is likely that dynamic interactions between the PFC and MTL were associated with successful performance on the dual N-back. Additionally, regions of the PFC activate during tasks of WM, attention and executive functioning, irrespective of stimuli type (Fletcher & Henson, 2001). Subsequently, our findings suggest that WM training recruited both PFC- and

MTL-dependent processes which led to transfer to EM in a process and stimulus non-specific fashion. Further neuroimaging investigations should examine this possibility and will be discussed in detail in section 5.4.4.

5.4.2. Transfer to G*f*

Our observation that spatial dual N-back training leads to improvements in G*f* (as measured by the BOMAT) replicates previous work that found G*f* improvement following practice on a dual N-back WM task involving auditory consonants and 2D visual locations (Jaeggi et al., 2008). Importantly, in line with our prediction, we have extended these findings by demonstrating that the monitoring of dual streams of information need not take place across two separate modalities; similar effects can be seen when participants focus on a single domain of information, in this case visual spatial stimuli. Our findings therefore add to the culminating evidence that the dual N-back training task is an effective cognitive stimulation tool which robustly leads to transfer on tasks of G*f*.

Although both the HG and LG groups improved significantly on the BOMAT in comparison to controls after training, the LG group made numerically greater gains on the BOMAT in contrast to the HG group (see Table 5-2). This is likely to be because the LG trainers possessed a numerically lower first assessment BOMAT score in comparison to the HG trainers (see Table 5-2). Subsequently, our data suggests that individuals with a lower pre-training G*f* make greater improvements following training. This is concordant with previous research that shows transfer is particularly evident in groups who have WM deficits (Holmes, Gathercole, & Dunning, 2009; Klingberg et al., 2005; Westerberg et al., 2007) and converges with the view that cognitive training primarily aids those who demonstrate a relatively lower level of cognitive functioning (Jaeggi et al., 2008; Morrison & Chein, 2011; Ranganath et al., 2011).

As discussed by Jaeggi and colleagues (2008), adaptive dual N-back WM training tasks may be particularly likely to induce G*f* improvements, because the WM training task and the BOMAT both require employment of a wide range of the same executive processes. These

include placing, updating and removing items in WM, inhibiting irrelevant information, monitoring performance, binding (for instance combining a scene with a location), as well as managing complex goals simultaneously. In addition, the N-back task, dual task processing, binding/chunking, as well as G*f* based tasks, all robustly activate a common neural network across the PFC and parietal cortex (Bor & Owen, 2007; Duncan, 2006; Gray, Chabris, & Braver, 2003). Based on the cognitive and neuronal associations between WM and G*f*, a recent hypothesis suggested WM and G*f* share the same common capacity constraint, in the number of items that can be held in WM, or the amount of interrelationships among elements in reasoning tasks (Halford, Cowan, & Andrews, 2007). Furthermore, individual differences in Raven's Advanced Progressive Matrices (RAPM; Raven, 1990), an analogous task to the BOMAT, have been accounted for through varying abilities to induce abstract relations and manage a large set of problem-solving goals in WM (Carpenter, Just, & Shell, 1990).

One criticism of the study by Jaeggi and colleagues (2008), which could also be leveled at the current investigation, was the decision to alter the standardized method for administering the BOMAT by reducing the time administered from 45 minutes to 10 minutes. In a recent commentary, Moody (2009), is deeply critical of Jaeggi and colleagues' (2008) decision to not sufficiently justify this change in task administration and brings into question whether this speeded version of the BOMAT successfully measures G*f*. For example, with only 10 minutes he suggests participants were unable to reach the more difficult items in this progressively difficult task and were not allowed time to learn about the test which would allow their performance to improve (Moody, 2009). In the current investigation, although we recognized it was not ideal for us to change the standardized administration of the BOMAT test, a decision was made to implement this alteration after careful consideration of evidence gathered from a pilot study. Our pilot study consisted of 10 participants who underwent an identical protocol to the current investigation except for the fact that G*f* was assessed before and after training using the RAPM (Raven, 1990) for 40 minutes. Preliminary results showed that the participants, who were primarily Oxford University students, performed so well on the

RAPM in their pre-training session that they had little room for improvement at the post-training session. It is interesting to note that no improvement on the RAPM, when the full administration time was allowed, was also found by Chein and Morrison (2010) in a group of participants who underwent extensive WM training. The authors attribute their failure to replicate Jaeggi and colleagues' (2008) findings to the large differences in the WM training task utilized. For example, the WM task used by Chein and Morrison (2010) required participants to maintain verbal or spatial information in the face of distraction whereas the dual N-back paradigm utilized by Jaeggi et al. (2008) placed a significant demand on complex binding processes and dual task management. In addition to this, however, Chein and Morrison (2010) also suggest that differences in the RAPM Matrices administration time might have led to their results conflicting with those of Jaeggi et al. (2008).

Neuropsychological tests, like the RAPM and the BOMAT, are designed as instruments to elucidate performance over a wide range of abilities, and are typically used in clinical settings to diagnose impairment associated with neurological injury or disorder. Subsequently, they are unlikely to be sufficiently sensitive to measure within-participant individual differences before and after training in a neurologically normal population. Considering this, we suggest that the null RAPM findings of our pilot study and that of Chein and Morrison (2010) occurred because individuals were able to achieve their maximum score on the RAPM in the pre-training session and therefore, could not improve after training because they had reached their personal ceiling. In a training study it is vital to make all assessment tasks challenging, so that improvement is possible and measurable within each participant from pre- to post-training. These findings and considerations motivated us to make 3 major changes to the pilot study for the present investigation in order to guard against ceiling effects; (1) a community sample was recruited so that there was no bias towards Oxford University students who may be more likely to score high on G*f* tests; (2) a more difficult G*f* task than the RAPM was used (i.e. the BOMAT); and finally, (3) the BOMAT was administered for just 10 minutes.

5.4.3. No transfer to Spatial Span and Scene Oddity

In this study neither the HG nor the LG training groups improved significantly on the spatial span or scene oddity tasks in comparison to controls. This is contrary to our predictions and indicates that training on the present WM task does not necessarily result in significant improvements in all tasks that are spatial and/or involve WM processes.

It is perhaps most surprising that no training-related improvement was observed on the spatial span tasks, considering that this test is expected to have overlapping cognitive and neuronal processes with the WM training task. However, previous studies have also failed to find that WM training transfers to non-trained WM tasks (Dahlin, Nyberg, et al., 2008; Owen et al., 2010), whereas others have shown that WM training leads to transfer to some, but not all non-trained WM tests (Buschkuehl et al., 2008; Dahlin, Neely, et al., 2008; Schmiedek et al., 2010). Inspection of our data (see Figure 5-5A), shows that trainers and controls both improved at the post-training session, with the HG trainers numerically improving the most, although this difference was not statistically significant. This large practice effect from pre-training to post-training session in all the participant groups irrespective of training was unexpected and it is possible that this may have masked a transfer effect which, if present, would be subtle.

A similar issue with practice effects was also observed on the oddity task, with all participant groups improving at the post-training session (Figure 5-5B). The scene oddity task is a challenging task of scene discrimination that requires individuals to decide which virtual reality room is the odd-one-out. We predicted that improvement on the scene WM training would transfer to the oddity test because both task involve spatial processing and subsequently should be supported by similar MTL regions (Lee, Buckley, et al., 2006; Lee & Rudebeck, 2010a). On the other hand, if one carefully considers the cognitive processes that support these two tests, it may be that they are too disparate for transfer to occur. For example, the scene oddity requires the participant to imagine and rotate themselves within three 3D virtual reality rooms over a 8 second time frame to discover which is the odd-one-out, whereas the

dual N-back requires them to monitor and recognise topographical scenes. Another possibility is that, as in the spatial span task, the large practice effects across all participants between session 1 and 2 (see Figure 5-5B), may have masked transfer to the oddity task in the training participants.

The explanation for why both the scene oddity and the spatial span tasks have particularly large practice effects at the post-training session is unknown. One possibility is that these tasks were particularly easy to create a strategy for between the pre- and post-training assessments, which led to increases in performance across all participants regardless of group. If this is the case, special care should be taken in the future to ensure all assessment tests are challenging and not easy to solve using a strategy. Another possibility is that both the spatial span and scene oddity tasks were performed in the second half of the 2 hour long assessment sessions. Previous investigators have warned against the use of multiple assessment tasks in cognitive training studies because they are susceptible to the confounds of participant boredom and exhaustion, which leads to the quality of assessment data diminishing over the session (Morrison & Chein, 2011). Therefore, perhaps these two tasks, which were placed at the end of the sessions, were particularly vulnerable to the influence of fatigue and poor effort. In this case, it might be beneficial to split the assessment sessions into 1 hour blocks in the future, with a considerable rest break in between.

5.4.4. General methodological issues and future directions

Despite the specific and unforeseen methodological issues discussed above, the current investigation was designed with care to minimize methodological confounds that would impede our ability to investigate training-related benefits. In particular, by creating an adaptive WM that was difficult to strategize for, and by asking participants to practice for 5 days a week for 4 weeks, we followed a number of recommendations indicating the importance of training participants: (1) on an adaptive protocol (Holmes et al., 2009; Klingberg et al., 2005); (2) on tasks that are difficult to complete using a strategy (Klingberg, 2010); and (3) for an extensive

amount of time (Jaeggi et al., 2008; Klingberg, 2010). In addition, feedback and results from our pilot study, suggested that motivation and compliance were also important factors to training success. Subsequently, the performance of each trainer was monitored and computed daily, and plotted against all other training participants on an interactive webpage. This was then scrutinized by the investigators, and those who appeared to be experiencing difficulties were contacted and provided with motivational tips.

Despite our best efforts to make our study as methodologically sound as possible, there are a few additional methodological issues which should be considered. Firstly, the current investigation had a passive control group, that is, the controls were not required to undergo any type of training in between their two assessment sessions. By including a control group in this study we are able to show that improvements on our cognitive tests following training were not merely due to test-retest effects. However, by not requiring them to engage in any type of training we were unable to rule out the possibility that the observed transfer effects may be explained by the training participants' effort or expectancy. For example, as in drug studies, the placebo effect could have caused our trainers to anticipate gains and therefore, put in more effort at the post-training session. In addition, the amount of cognitive investment during the training period, adherence to the training schedule, use of a computer, and amount of interaction with the investigators may also have affected the trainers' post-test performance in a non-specific manner (Buschkuehl & Jaeggi, 2010; Klingberg, 2010; Morrison & Chein, 2011). To circumvent these issues of expectancy and effort, it would have been preferable to include an 'active control group', who engaged in a believable training regime, so controls had the same motivation levels, contact with computers and interaction with scientific staff (Buschkuehl & Jaeggi, 2010; Morrison & Chein, 2011; Ranganath et al., 2011). However, as WM training studies are logistically very challenging, expensive, and time consuming to run, only a handful of previous investigations have used active control groups (Holmes et al., 2009; Jaeggi et al., 2011; Klingberg et al., 2005; Owen et al., 2010). The prevalent practice, as in this study, is to compare the trainers to a non-active or passive control group (Buschkuehl et al.,

2008; Dahlin, Neely, et al., 2008; Dahlin, Nyberg, et al., 2008; Jaeggi et al., 2008; Olesen et al., 2004; Schmiedek et al., 2010) . Although it is ideal for the control group in a cognitive training study to be active, its omission does not necessarily discredit our findings. Thorell and colleagues (Thorell, Lindqvist, Bergman Nutley, Bohlin, & Klingberg, 2009) recently demonstrated no differences in performance gains between a passive and active control group, which suggests that the former approach is adequate. Additionally, in our study the LG training group almost functions as an active control, as they trained for the same amount of time as the HG group and were thus exposed to the same expectancy and effort effects. Critically, however, the LG group's performance was not significantly different from the passive control group on any transfer tasks in the post-training session. In the future, if logistically possible, an active control group should be included and trained on a computer for the same amount of time as our training group (20 minutes a day, 5 days a week for 4 weeks). The active controls' 'training' task would need to be cognitively engaging but lacking the critical intervention factor (i.e. complex spatial WM) to control for expectancy/effort effects. Perhaps, therefore, a knowledge or vocabulary based test could be designed and utilized for the controls to train on (Jaeggi et al., 2011; Owen et al., 2010),.

Another issue that was not investigated in our study due to practical limitations was the long-term effects of WM training - although we found transfer from WM to EM in HG trainers after 4 weeks of intensive training, we do not know how long these improvements last. There is currently little consensus as to how long WM or executive functioning training-related benefits are maintained, with some suggesting they persist for 2-3 months (Jaeggi et al., 2011; Li et al., 2008), whilst others show that they are still observable after 18 months (Dahlin, Nyberg, et al., 2008). In future investigations, thorough assessment of the long-term maintenance of WM training benefits could be carried out by additional assessments at 3 months and then 1 year. In addition, the possibility that booster training sessions might be useful in maintaining improvement performance could be examined (Ball et al., 2002; Salthouse, 2006), by splitting the training group in half and asking one group to do additional

WM training and the other half not to. For this to occur additional experimental resources would need to be available and careful planning at the recruitment stage would be crucial to ensure participants could be retained for follow up over a few years.

Due to time constraints on the assessment sessions, it was not possible to assess the participants' abilities on other EM tasks, such as, prose or shape recall. If the observed recognition memory transfer effects are, indeed, mediated by MTL stimulation (as suggested above), it is possible that WM training may lead to improvements in other measures of EM in the HG group. On the other hand, Jonides (2004) postulates that for transfer to occur, the training and transfer tasks must share neural *and* cognitive constructs (Jonides, 2004). It is conceivable, therefore, that EM recall tests that use words and shapes may require cognitive abilities that are too divergent from those necessary for spatial WM training tasks, therefore minimising the possibility of successful transfer. In the future we could explore if spatial WM training leads to EM improvement in a wider range of EM tests, such as the Logical Memory subtest of the WMS-III and the shape and name recall from the Doors and People, by carrying out multiple pre- and post-training assessment sessions.

Finally, an obvious follow-up to this investigation would be to carry out the training study in conjunction with neuroimaging of the trainers and controls at the pre- and post-training assessment sessions. fMRI could be used to examine the activity during the WM training task and/or the EM transfer tests. A previous fMRI study of an N-back task of complex spatial scenes showed activations within the posterior hippocampus and parahippocampal cortex, with increasing activity in the same regions for 2- versus 1-back (Lee & Rudebeck, 2010a). In addition to this, a meta-analysis of 24 fMRI N-back studies revealed consistent activations within the premotor cortex, dorsolateral and ventrolateral PFC and posterior parietal cortex (Owen, McMillan, Laird, & Bullmore, 2005), while the dual N-back paradigm has been shown to activate the same regions as the single N-back paradigm, with the additional recruitment of the bilateral parahippocampal gyri and middle frontal gyrus (Yoo, Paralkar, & Panych, 2004). With these previous findings in mind, one would expect pre-training scanning of

our WM task to reveal significant activity within the MTL regions involved in complex spatial processing and WM such as the hippocampus and parahippocampal cortex, with additional activity in the dorsolateral and ventrolateral PFC, and parietal regions. It is difficult to predict how this pattern of activation may change following training - for example, whilst some studies have found decreased levels of activity following training (Schneiders, Opitz, Krick, & Mecklinger, 2011) due to suggested increased neural efficiency (Kelly, Foxe, & Garavan, 2006), others have reported the opposite and observed increased activity after WM training (Erickson et al., 2007; Olesen et al., 2004). Carrying out scanning of the scene and object ROC transfer tasks before and after training would also elucidate the neural mechanisms by which the transfer between WM and EM occurred. Previous investigations show that scene and object recognition memory tasks lead to activations within the bilateral hippocampus, posterior parahippocampal gyrus, perirhinal cortex, parietal cortices and PFC (e.g. Davachi et al., 2003; Ranganath et al., 2004; Montaldi et al., 2006; Diana et al., 2009), areas that are also predicted to be activated during spatial dual N-back. If overlapping patterns of activity were seen in association with the WM training and EM tasks, for example in the hippocampus and PFC, this would support Jonides' (2004) postulation that for transfer to happen, training and transfer tasks must be supported by the same neural activations.

Changes in the functional connectivity and white matter integrity of the whole brain following WM training could also be explored. One previous DTI investigation showed that 2 months of dual N-back training led to increases in FA within a white matter tract close to the intraparietal sulcus and corpus callosum (Takeuchi et al., 2010). This white matter tract is suggested to be implicated in neural networks that connect the prefrontal and parietal lobes, regions that have been associated with increased activity after WM training (Olesen et al., 2004). Interestingly, one potential mechanism behind the increased FA is the induction of myelination, caused by neural activity in the fibers tracts during WM training (Takeuchi et al., 2010). Keeping this in mind, as well as the likely regions of neural activity associated with the current WM training task, one prediction is that training on the present WM task will lead to an

increase in FA in the major tracts of the MTL, for example the fornix, cingulum and mammilo-thalamic tract, and the white matter connections between the MTL and PFC, such as the uncinate fasciculus.

At present, no previous studies have investigated the effect of WM training on the functional connectivity of brain regions or RSNs of the brain. Connectivity strength, however between the PFC and MTL regions has been shown to be positively correlated with performance on a WM task (Campo et al., 2012) and coherence within the DMN is positively associated with WM and intellectual abilities (Hampson, Driesen, Skudlarski, Gore, & Constable, 2006; Song et al., 2008). It may, therefore, be conceivable that individual differences in task proficiency following WM training may cause changes in the functional connectivity of the brain (Buschkuehl, Jaeggi, & Jonides, 2012). In the light of the fMRI predictions made above, it may be expected that functional connectivity between the PFC and MTL regions will increase post-training. What is more, there may be increases in co-activation within RSNs that encompass the hippocampus, parahippocampal gyrus, perirhinal cortex and PFC (i.e. the ECN, DMN and PHN) following WM training.

Chapter 6 - General Discussion

The first aim of this thesis was to determine the functional role of the fornix in recognition memory using DTI, a relatively novel neuroimaging technique. The results of this study increased our knowledge of the white matter and functional connectivity of the MTL and their role in LTM processes, and this theme was subsequently pursued further in the remainder of my thesis. After investigating if the findings from Chapter 2 could be replicated when recall and recognition were measured using a battery of neuropsychological tests, I explored the consequences of subcortical damage of the MTL regions on the functional networks and white matter fibre tracts of the MTL using Rs-fMRI and DTI in 2 amnesic patients. Finally, as a starting point to understand the underlying mechanisms of the correlational findings between memory performance and fornix microstructural integrity in Chapters 2 and 3, a cognitive training study was carried out to probe if long-term declarative memory processes such as recognition memory could be improved through extensive cognitive training. In this chapter, I will first briefly summarize the results of Chapters 2-5. Next, I will discuss a few general methodological issues in regards to DTI neuroimaging. Finally, some possible future directions, with a particular focus on those with clinical applications, will be proposed.

6.1. Summary of Results

In Chapter 2, DTI was used to investigate whether the microstructural integrity of the fornix in neurologically healthy young individuals was related to DPSD (i.e. recollection and familiarity) or UVSD (i.e. slope of z-ROC curve and sensitivity) estimates of performance on a scene and object ROC recognition memory task. To ensure that any observed effects were specific to LTM abilities, two control tasks were also included to measure the participants' ability on a colour discrimination task and an attention task. As DTI was a relatively new neuroimaging technique at the time of the study and the fornix is a region of low FA, some methodological issues

pertaining to partial volume errors were encountered during the data analysis. To correct for these issues a number of complementary analyses were conducted including TBSS, probabilistic tractography with mean FA extraction, partial volume correction and white matter VBM.

All these analyses consistently revealed that the integrity of the fornix, as measured by FA, correlated significantly with DPSD performance estimates of recollection but not those of familiarity. In addition, there was a suggestion of an effect of stimulus type, with a more significant relationship between scene recollection and fornix FA than that between object recollection and fornix FA. On the other hand, no relationship was found between fornix microstructure and memory performance when behaviour was modelled by the UVSD model of recognition memory (i.e. slope and sensitivity) or performance on non-mnemonic tasks of colour discrimination and motor attention controls.

These results lend further support to a dual-process view of MTL function - that distinct pathways between the MTL and medial diencephalon are involved with different memory processes (Aggleton & Brown, 1999; Yonelinas, 1994). As the fornix is the major efferent of the hippocampus and damage to it in humans and non-human primates leads to dense memory deficits (e.g. Gaffan and Gaffan, 1991; Aggleton et al., 2000), it has been suggested this tract can be regarded as a functional extension of the hippocampus formation (Aggleton & Brown, 1999). The data from Chapter 2 support the view that the hippocampus and its interactions with the mammillary bodies and anterior thalamus via the fornix support recollection but not familiarity memory (Aggleton, Vann, Denby, et al., 2005; Davachi et al., 2003; Ranganath et al., 2004; Yonelinas et al., 2002). Furthermore, by also ruling out any relationship between UVSD model estimates of recognition memory performance (i.e. slope of z-ROC curve and sensitivity), we were able discount the possibility that memory strength is a more critical process in the involvement of the hippocampus and its fibre tracts in recognition memory (Squire et al., 2004, 2007) than the type of recognition memory process.

Next, Chapter 3 explored whether the findings from Chapter 2 could be extended using standard neuropsychological tests of recall and recognition to assess individual differences. It is important to determine if standardized tasks are a suitable tool to measure differences between neurologically intact healthy participants as they are widely utilized in the recognition memory literature to assess differences within young adults, older adults and patients (e.g. Nestor et al., 2007; Tsivilis et al., 2008; Charlton et al., 2009; Metzler-Baddeley et al., 2011). After testing the participants from Chapter 2 on a standard battery of psychometric tests, it was found that some measures of recall (e.g. Doors and People recall, WMS-III Logical Memory delayed recall and WMS-III Family Pictures immediate recall) correlated with FA in the fornix tail. This gave support to previous DTI research (Metzler-Baddeley et al., 2011; Nestor et al., 2007) and the idea that the fornix is important for recollection but not familiarity memory (Aggleton & Brown, 1999). It is important to note, however, that not all measures of recall correlated with fornix FA and furthermore, some tests of recognition (e.g. Recognition Memory Test faces) were associated with large clusters of correlation in the fornix. What is more, not all TBSS and tractography findings were consistent with one another, a potential problem considering the partial volume issues experienced in Chapter 2. These results indicate that the use of standard tests of episodic memory to measure individual differences in neurologically intact young adults may be an inappropriate method to investigate specific memory processes such as recollection and familiarity. In addition, these findings highlight the importance of using mnemonic tests that consistently and reliably measure the cognitive construct of interest when examining the relationship between individual differences in white matter microstructure and mnemonic ability.

Despite the increasing use of DTI and Rs-fMRI neuroimaging techniques, the consequences of focal MTL damage on the structural and functional networks of the brain have been relatively under-investigated. Chapter 4, therefore, used these techniques and white matter voxel based morphometry to investigate the impact of bilateral damage to the MTL structures in two patients on the white matter micro and macrostructure integrity and the

resting-state networks of the brain. The two amnesic individuals' DTI and Rs-fMRI data were compared to a group of 32 age- and education-matched controls at the whole brain level. Two complementary region of interest DTI analyses (e.g. TBSS and probabilistic tractography) were also carried out on two of the major white matter fibre tracts of the MTL and temporal lobe, the fornix and the left and right uncinate fasciculus.

The DTI results showed that patient MTL3, who has extensive damage to the bilateral MTL regions, had reduced white matter integrity in the fornix and the right uncinate fasciculus in contrast to controls, but only a trend towards a significant reduction in gross white matter morphometry of the MTL. What is more, Rs-fMRI data revealed that she had significantly reduced connectivity of a number of brain regions (e.g. parahippocampal cortex, posterior hippocampus and thalamus in the right hemisphere) in relation to the parahippocampal network, a resting-state network first discovered by Trachtenberg et al. (2011). Patient HC3, on the other hand, who has focal damage circumscribed to the bilateral hippocampus, had no reduction in resting state connectivity or macrostructure of the white matter. TBSS and tractography, however, did reveal a trend towards a reduction in patient HC3's fornix, but not left or right uncinate fasciculus, FA in contrast controls.

These results suggest that neither amnesic individual has obvious functional connectivity disruption between brain areas, nor macro- or microstructural white matter atrophy outside the MTL, even in the presence of extensive brain damage (i.e. patient MTL3). Although it is possible that the small number of patients may have resulted in a lack of sensitivity, these results are a first step in exploring the consequences of medial temporal lobe damage on the wide ranging functional and structural networks of the brain. In addition, they undermine the idea that some of the cognitive deficits demonstrated by patients with focal MTL damage, particularly those pertaining to higher-order stimulus perception, may be due to damage beyond the MTL (e.g. Suzuki, 2009).

Finally, one interesting question that was raised by the findings of Chapter 2 is the

direction of the relationship between fornix microstructural integrity and recollection ability. For example, it is unknown if the innate existence of better fornix microstructure leads to a higher recollection ability, or conversely, if the improvement of an individual's recollection over time may cause an enhancement in fornix FA. The first step to investigate this question was to determine if extensive cognitive training could indeed lead to increases in long-term declarative memory processes such as recollection and familiarity. To this end, a dual N-back working memory task was adapted to emphasise spatial processing by asking participants to monitor both the location and identity of scene images. This adjustment was made in an effort to place a demand on MTL regions, in particular the hippocampus, to maximise the possibility that transfer of ability on a spatial WM task would also lead to improvements on test of episodic memory. A group of 27 young adults trained on the spatial dual N-back for 20 minutes a day, 5 days a week for 4 weeks. Assessment sessions took place before and after training and consisted of a battery of cognitive tasks: the scene N-back training task, the Bochumer Matrices-Test (BOMAT) (Hossiep et al., 1999), scene and object recognition ROC memory tests, spatial span and the scene oddity paradigm (Lee, Buckley, et al., 2005). The age- and education-matched control group took the pre- and post-assessment sessions 28 days but and did not carry out any type of cognitive stimulation training in between.

The results showed that the quality of training, that is how much the trainers improved during their 20 days of training had significant effects on transfer to episodic memory. Participants were split into high and low gain groups based on their performance during training and compared to controls. The high gain trainers showed a significant improvement on both the episodic memory tasks in comparison to low gain trainers and controls. In addition to this, in line with previous research (Jaeggi et al., 2008), training on the dual N-back also lead to improvement on a task of fluid intelligence (e.g. the BOMAT) in all participants regardless of training performance. These findings are significant as this is one of the first instances of improvement on a single cognitive training task transferring to tasks of episodic memory. What is more, the findings from this chapter further support the notion that individual differences in

training performance can have a large impact on the likelihood of transfer (Buschkuehl & Jaeggi, 2010; Jaeggi et al., 2011; Morrison & Chein, 2011; Ranganath et al., 2011). Since the results from Chapter 5 have established that episodic memory can be improved through cognitive training, the next step of this project can be implemented, with DTI scanning to be conducted before and after spatial WM training to determine the affects on the white matter of the brain and specifically the fornix.

6.2. General Limitations

Although DTI is currently the predominant neuroimaging technique used to explore the white matter fibre tracts of the brain a number of general limitations are associated with this technique that impacted the results of this thesis. Tractography analyses of DTI data reveal the path of least resistance to water diffusion within the brain, which is taken to represent a white matter fibre tract. It is important to note, however, that tractography does not provide the anatomical accuracy that other invasive techniques can provide, for instance the injection of tracers into the monkey or rodent brain. This means that pathways discovered by tractography sometimes do not successfully correspond to a underlying fibre pathways (Johansen-Berg & Behrens, 2006). Issues with this were experienced particularly in Chapters 2 and 3 where it was necessary for the fornix tractography results for each participant to be checked manually to ensure that no fibres beyond the fornix were included. To ensure these issues were not experienced in Chapter 4 the tractography methods were altered in an effort minimise the possibility of false positives, reduce the need for manual editing and to standardize the pathways which extracted FA across participants.

Another issue commonly experienced in all neuroimaging techniques is that that voxels are a number of millimetres cubed (e.g. 1.0 x 1.0 x 1.0 mm) which means that they are likely to represent many thousands of axons. This is not overly problematic until small tracts, like the fornix which are surrounded by other white matter like the internal capsule, are examined using tractography or TBSS. In these instances, some of the assumptions that TBSS and

tractography algorithms make, for example that each voxel is well characterised by a single orientation estimate, can perform sub-optimally due to crossing fibres within a voxel (Johansen-Berg & Behrens, 2006). Due to these issues, a number of complementary analysis techniques were utilized in this thesis and strong conclusions were only made when all analysis strategies yielded the same results. In the future, however, if DTI is to become a more widely used neuroimaging technique in both research and clinical settings, analysis techniques will need to become more reliable and less prone to false positives and negatives.

Finally, DTI is unable to provide anatomical information about the white matter fibre pathways it explores. For example, it cannot reveal the directionality of the connections (i.e. anterograde or retrograde), the location of synapses and most importantly of all, if the fibre pathways are still functional. This latter issue is of particular note in regards to the findings from Chapter 4, although it is somewhat unlikely that non-functional white matter bundles would remain intact and unaffected by degeneration processes within the brain. Whilst these limitations of DTI should be noted, it is currently the most commonly used neuroimaging technique available that allows the integrity of the white matter of the brain to be explored. As with any relatively new neuroimaging technique, however, its results should be checked carefully and treated with caution particularly in regions of low FA, as they were in the current thesis, until analysis techniques become more reliable.

6.3. Future Directions and Applications

Cognitive neuroscience is an ever expanding research field where novel, complex and relatively expensive methods, like DTI and Rs-fMRI described in this thesis, are used to explore the functions of the brain. For example considering MTL research alone, there have been a vast number of studies published over the past twenty years that have used these novel techniques to investigate MTL function, and these are in addition to the large bodies of research that have been conducted using invasive techniques in non-human animals. Notably, while significant advances have been made in our understanding of the cognitive functions of individual MTL

structures, the clinical relevance of many of these findings remains relatively under-explored. This is a critical point considering the debilitating nature of memory loss or amnesia that can often occur after traumatic head injury, stroke, viral illness or as a result of dementia such as Alzheimer's disease (AD). Indeed, the number of people with dementia alone is expected to rise to 1 million by 2021 (http://alzheimers.org.uk). With this in mind, the current thesis, in particular the investigations described in Chapters 4 and 5, were designed to not only answer interesting and important cognitive neuroscientific questions but also, to potentially speak to some aspects of patient care and rehabilitation.

In Chapter 5, I described a cognitive training program that was able to stimulate episodic LTM improvement when certain conditions were met (i.e. when participants improved successfully at the training task). This result is not only interesting in the context of investigating the causal direction of the relationship between fornix microstructural integrity and recollection ability, but it also has clear implications for memory rehabilitation. One possibility for the future is for the spatial dual N-back task to be used in cognitive training investigations in healthy elderly adult participants and memory impaired brain damaged patients such as cases with mild cognitive impairment or non-progressive lesions to the MTL. It is likely that a number of changes will have to be made to the training task to make it suitable for these participant populations. For example, the scene stimuli may have to be presented for longer durations to give the participants a greater amount of time to respond to the N-back repetitions, and subsequently, the length of trials may have to be adjusted. Furthermore, piloting will be necessary to determine if the training sessions need to be split into shorter segments in order to minimize fatigue effects, or if additional reminder cues of task instructions have to be presented on the screen throughout testing, particularly for the memory impaired patients. After making the necessary methodological adjustments, it would be extremely interesting to see if improvements in long term declarative memory can be observed in elderly adults and amnesic patients after a period of training on the spatial dual N-back paradigm. If this were the case then this knowledge could be used to further inform treatment strategies for

individuals with memory loss or those vulnerable to memory difficulties (i.e. aging adults).

Since the 19th century the brain has been predominantly investigated with regards to functional specialization, in which precise functions are assigned to discrete brain structures. It is well accepted, however, that brain structures do not function in isolation from each other and are communicating constantly via many thousands of axons to form extensive functional networks. The recent advent of DTI and functional connectivity fMRI techniques has made it possible to study these networks of interacting regions and there has been increasing interest in how these neuroimaging techniques can be applied in clinical settings (Fox & Greicius, 2010; Johansen-Berg & Behrens, 2006; Rosazza & Minati, 2011).

Techniques such as DTI and Rs-fMRI are particularly suitable for clinical settings because patients are not required to engage in a task within the scanner and can even be unconscious. The study described in Chapter 4 revealed that patients with static lesions to the MTL damage do not necessarily have damage to white fibre tracts and functional networks beyond the MTL. It was suggested that this indicates that patients MTL3 and HC3 could benefit from rehabilitation strategies that take advantage of preserved frontal and parietal lobe functions, for example, they may profit from memory aids which help them plan, take notes and keep diaries to help compensate for their gross memory impairment. Future research, however, is needed before it can be fully appreciated if resting-state connectivity of the brain can help predict rehabilitation outcomes and guide patient treatment. For example, with regards to amnesic individuals with focal MTL lesions, a study could be conducted in which Rs-fMRI and DTI scans, and a detailed neuropsychological assessment are carried out soon after brain injury. All patients would then be given access to the same cognitive rehabilitation program for instance, a specific memory strategy training program targeting the use of executive processes to facilitate the encoding and retrieval of memoranda. At the end of 3 years it could then be determined whether there was a relationship between cognitive outcome and the resting-state, white matter and cognitive neuropsychological assessments carried out prior to treatment. It is possible that the patients who benefit most from the

memory strategy training program will be those who had relatively intact structural and functional connectivity between the MTL and prefrontal cortex regions immediately after brain injury. Findings of studies such as this could encourage Rs-fMRI and DTI neuroimaging to be included in diagnostic assessment in the future. What is more, they may help clinicians to assign patients to treatment programs that are more likely to be of benefit to them.

Finally, although the use of DTI has allowed us to make considerable progress in our understanding of the behavioural relevance of major white matter tracts, much still remains unknown. It is important, therefore that future DTI investigations continue this endeavour by scanning groups of participants, testing them on batteries of cognitive, psychiatric and/or motor tasks, and then using analysis techniques like TBSS to explore the relationship between FA variability in specific tracts and behavioural performance scores. Results of such work would not only further our knowledge on the functional role of the major pathways of the brain but could also have important implications for patient care. For example, probabilistic tractography could be performed in patients prior to neurosurgery to ensure that important functional tracts are not bisected during the surgical procedure and subsequently, minimise any unnecessary impact on cognitive functioning.

References

Adcock, J. E., Wise, R. G., Oxbury, J. M., Oxbury, S. M., & Matthews, P. M. (2003). Quantitative fMRI assessment of the differences in lateralization of language-related brain activation in patients with temporal lobe epilepsy. *NeuroImage*, 18(2), 423–438.

Aggleton, J. P. (1986). A description of the amygdalo-hippocampal interconnections in the macaque monkey. *Experimental Brain Research*, 64(3), 515–526.

Aggleton, J. P. (2008). EPS Mid-Career Award 2006: Understanding anterograde amnesia: disconnections and hidden lesions. *The Quarterly Journal of Experimental Psychology*, 61(10), 1441–1471.

Aggleton, J. P., & Brown, M. W. (1999). Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behavioral and Brain Sciences*, 22(3), 425–489.

Aggleton, J. P., & Brown, M. W. (2006). Interleaving brain systems for episodic and recognition memory. *Trends in Cognitive Sciences*, 10(10), 455–463.

Aggleton, J. P., McMackin, D., Carpenter, K., Hornak, J., Kapur, N., Halpin, S., Wiles, C. M., et al. (2000). Differential cognitive effects of colloid cysts in the third ventricle that spare or compromise the fornix. *Brain*, 123(4), 800–815.

Aggleton, J. P., & Pearce, J. M. (2001). Neural systems underlying episodic memory: insights from animal research. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 356(1413), 1467–1482.

Aggleton, J. P., & Shaw, C. (1996). Amnesia and recognition memory: a re-analysis of psychometric data. *Neuropsychologia*, 34(1), 51–62.

Aggleton, J. P., Vann, S. D., Denby, C. E., Dix, S., Mayes, A. R., Roberts, N., & Yonelinas, A. P. (2005). Sparing of the familiarity component of recognition memory in a patient with hippocampal pathology. *Neuropsychologia*, 43(12), 1810–1823.

Aggleton, J. P., Vann, S. D., & Saunders, R. C. (2005). Projections from the hippocampal region to the mammillary bodies in macaque monkeys. *European Journal of Neuroscience*, 22(10), 2519–2530.

Agosta, F., Pievani, M., Geroldi, C., Copetti, M., Frisoni, G. B., & Filippi, M. (2012). Resting state fMRI in Alzheimer's disease: beyond the default mode network. *Neurobiology of Aging*, 33(8), 1564–1578.

Agostini, A., Filippini, N., Cevolani, D., Agati, R., Leoni, C., Tambasco, R., Calabrese, C., et al. (2011). Brain functional changes in patients with ulcerative colitis: a functional magnetic resonance imaging study on emotional processing. *Inflammatory bowel diseases*, 17(8), 1769–1777.

Allegri, R. F., Drake, M., & Thomson, A. (1999). Neuropsychological findings in patients with middle temporal lobe epilepsy. *Revista de neurologia*, 29(12), 1160–1163.

Aminoff, E., Gronau, N., & Bar, M. (2007). The parahippocampal cortex mediates spatial and nonspatial associations. *Cerebral Cortex*, 17(7), 1493–1503.

Andersen, S. M., Rapcsak, S. Z., & Beeson, P. M. (2010). Cost function masking during normalization of brains with focal lesions: still a necessity? *NeuroImage*, 53(1), 78–84.

Andersson, J. L. R., Jenkinson, M., & Smith, S. M. (2007a). Non-linear registration, aka spatial normalisation . *FMRIB Analysis Group Technical Reports:TR07JA2*.

Andersson, J. L. R., Jenkinson, M., & Smith, S. M. (2007b). Non-linear optimisation. *FMRIB Analysis Group Technical Reports:TR07JA1*.

Andrade, J. (2001). *Working Memory in Context*. Hove, UK: Psychology.

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry--the methods. *NeuroImage*, 11(6), 805–821.

Assaf, B. a, Mohamed, F. B., Abou-Khaled, K. J., Williams, J. M., Yazeji, M. S., Haselgrove, J., & Faro, S. H. (2003). Diffusion tensor imaging of the hippocampal formation in temporal lobe epilepsy. *American Journal of Neuroradiology*, 24(9), 1857–1862.

Atkinson, R. C., & Shiffrin, R. M. (1968). Human memory: A proposed system and its control processes. In K. W. Spence (Ed.), *The Psychology of Learning and Motivation: Advances in Research and Theory.* (pp. 89–195). New York, NY: Academic Press.

Awipi, T., & Davachi, L. (2008). Content-specific source encoding in the human medial temporal lobe. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 34(4), 769–779.

Baddeley, A. D. (1986). *Working Memory*. Oxford, UK: Oxford University Press.

Baddeley, A. D. (2000). The episodic buffer: a new component of working memory? *Trends in Cognitive Sciences*, 4(11), 417–423.

Baddeley, A. D. (2003). Working memory: looking back and looking forward. *Nature Reviews Neuroscience*, 4(10), 829–839.

Baddeley, A. D., Emslie, H., & Nimmo-Smith, I. (2006). *Doors and People*. Bury St Edmunds (UK): Thames Valley Test Company.

Baddeley, A. D., & Hitch, G. J. (1974). Working Memory. In G. A. Bower (Ed.), *Recent Advances in Learning and Motivation.* (pp. 47–89). New York, NY: Academic Press.

Baddeley, A. D., Vargha-Khadem, F., & Mishkin, M. (2001). Preserved recognition in a case of developmental amnesia: implications for the acquisition of semantic memory? *Journal of Clinical Neuroscience*, 13(3), 357–369.

Baddeley, A. D., & Warrington, E. K. (1970). Amnesia and the distinction between long- and short-term memory. *Journal of Verbal Learning and Verbal Behavior*, 9, 176–189.

Bai, F., Zhang, Z., Yu, H., Shi, Y., Yuan, Y., Zhu, W., Zhang, X., et al. (2008). Default-mode network activity distinguishes amnestic type mild cognitive impairment from healthy aging: a combined structural and resting-state functional MRI study. *Neuroscience letters*, 438(1), 111–115.

Ball, K., Berch, D. B., Helmers, K. F., Jobe, J. B., Leveck, M. D., Marsiske, M., Morris, J. N., et al. (2002). Effects of Cognitive Training Interventions With Older Adults. *The Journal of the American Medical Association*, 288(18), 2271–2281.

Bar, M., Aminoff, E., & Schacter, D. L. (2008). Scenes unseen: the parahippocampal cortex intrinsically subserves contextual associations, not scenes or places per se. *The Journal of Neuroscience*, 28(34), 8539–8544.

Barense, M. D., Bussey, T. J., Lee, A. C. H., Rogers, T. T., Davies, R. R., Saksida, L. M., Murray, E. A., et al. (2005). Functional specialization in the human medial temporal lobe. *The Journal of Neuroscience*, 25(44), 10239–10246.

Barense, M. D., Gaffan, D., & Graham, K. S. (2007). The human medial temporal lobe processes online representations of complex objects. *Neuropsychologia*, 45(13), 2963–2974.

Barense, M. D., Henson, R. N., Lee, A. C. H., & Graham, K. S. (2010). Medial temporal lobe activity during complex discrimination of faces, objects, and scenes: Effects of viewpoint. *Hippocampus*, 20(3), 389–401.

Barense, M. D., Ngo, J. K. W., Hung, L. H. T., & Peterson, M. A. (2011). Interactions of Memory and Perception in Amnesia: The Figure-Ground Perspective. *Cerebral Cortex*, 1–12.

Barense, M. D., Rogers, T. T., Bussey, T. J., Saksida, L. M., & Graham, K. S. (2010). Influence of conceptual knowledge on visual object discrimination: insights from semantic dementia and MTL amnesia. *Cerebral Cortex*, 20(11), 2568–2582.

Bartko, S. J., Winters, B. D., Cowell, R. A., Saksida, L. M., & Bussey, T. J. (2007). Perirhinal cortex resolves feature ambiguity in configural object recognition and perceptual oddity tasks. *Learning & Memory*, 14, 821–832.

Basser, P. J., Mattiello, J., & Le Bihan, D. (1994). Estimation of the effective self-diffusion tensor from the NMR spin echo. *Journal of Magnetic Resonance, Series B*, 103(3), 247–254.

Baxter, M. G. (2009). Involvement of medial temporal lobe structures in memory and perception. *Neuron*, 61(5), 667–677.

Bayley, P. J., Gold, J. J., Hopkins, R. O., & Squire, L. R. (2005). The neuroanatomy of remote memory. *Neuron*, 46(5), 799–810.

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR in Biomedicine*, 15(7-8), 435–455.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for Beck Depression Inventory II (BDI-II).* San Antonio, TX: Psychology Corporation.

Beckmann, C. F., DeLuca, M., Devlin, J. T., & Smith, S. M. (2005). Investigations into resting-state connectivity using independent component analysis. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 360(1457), 1001–1013.

Behrens, T. E. J., Berg, H. J., Jbabdi, S., Rushworth, M. F. S., & Woolrich, M. W. (2007). Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? *NeuroImage*, 34(1), 144–155.

Behrens, T. E. J., Johansen-Berg, H., Woolrich, M. W., Smith, S. M., Wheeler-Kingshott, C. A., Boulby, P. A., Barker, G. J., et al. (2003). Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nature Neuroscience*, 6(7), 750–757.

Behrens, T. E. J., Woolrich, M. W., Jenkinson, M., Johansen-Berg, H., Nunes, R. G., Clare, S., Matthews, P. M., et al. (2003). Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magnetic Resonance Imaging*, 50(5), 1077–1088.

Bilir, E., Craven, W., Hugg, J. W., Gilliam, F., Martin, R., Faught, E., & Kuzniecky, R. I. (1998). Volumetric MRI of the limbic system: anatomic determinants. *Neuroradiology*, 40(3), 138–144.

Bird, C. M., & Burgess, N. (2008a). The hippocampus and memory: insights from spatial processing. *Nature Reviews Neuroscience*, 9(3), 182–194.

Bird, C. M., & Burgess, N. (2008b). The hippocampus supports recognition memory for familiar words but not unfamiliar faces. *Current Biology*, 18(24), 1932–1936.

Bird, C. M., Shallice, T., & Cipolotti, L. (2007). Fractionation of memory in medial temporal lobe amnesia. *Neuropsychologia*, 45(6), 1160–1171.

Bird, C. M., Vargha-Khadem, F., & Burgess, N. (2008). Impaired memory for scenes but not faces in developmental hippocampal amnesia: a case study. *Neuropsychologia*, 46(4), 1050–1059.

Biswal, B. B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional Connectivity in the Motor Cortex of Resting Human Brain using Echo-Planar MRI. *Magnetic Resonance Imaging*, (9), 537–541.

Bohbot, V. D., Iaria, G., & Petrides, M. (2004). Hippocampal function and spatial memory: evidence from functional neuroimaging in healthy participants and performance of patients with medial temporal lobe resections. *Neuropsychology*, 18(3), 418–425.

Boly, M., Phillips, C., Tshibanda, L., Vanhaudenhuyse, a, Schabus, M., Dang-Vu, T. T., Moonen, G., et al. (2008). Intrinsic brain activity in altered states of consciousness: how conscious is the default mode of brain function? *Annals of the New York Academy of Sciences*, 1129, 119–129.

Boly, M., Tshibanda, L., Vanhaudenhuyse, A., Noirhomme, Q., Schnakers, C., Le Doux, D., Boveroux, P., et al. (2009). Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. *Human Brain Mapping*, 30(8), 2393–2400.

Bor, D., Duncan, J. S., & Owen, A. M. (2001). The role of spatial configuration in tests of working memory explored with functional neuroimaging. *Scandinavian Journal of Psychology*, 42(3), 217–224.

Bor, D., Duncan, J. S., Wiseman, R. J., & Owen, A. M. (2003). Encoding strategies dissociate prefrontal activity from working memory demand. *Neuron*, 37(2), 361–367.

Bor, D., & Owen, A. M. (2007). Cognitive Training: Neural Correlates of Expert Skills. *Current Biology*, 17(3), 95–97.

Bowles, B., Crupi, C., Mirsattari, S. M., Pigott, S. E., Parrent, A. G., Pruessner, J. C., Yonelinas, A. P., et al. (2007). Impaired familiarity with preserved recollection after anterior temporal-

lobe resection that spares the hippocampus. *Proceedings of the National Academy of Sciences of the United States of America*, 104(41), 16382–16387.

Braak, H., Alafuzoff, I., Arzberger, T., Kretzschmar, H., & Del Tredici, K. (2006). Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta neuropathologica*, 112(4), 389–404.

Braak, H., & Braak, E. (1996). Development of Alzheimer-related neurofibrillary changes in the neocortex inversely recapitulates cortical myelogenesis. *Acta neuropathologica*, 92(2), 197–201.

Brasted, P. J., Bussey, T. J., Murray, E. A., & Wise, S. P. (2003). Role of the hippocampal system in associative learning beyond the spatial domain. *Brain*, 126(5), 1202–1223.

Brett, M., Leff, a P., Rorden, C., & Ashburner, J. (2001). Spatial normalization of brain images with focal lesions using cost function masking. *NeuroImage*, 14(2), 486–500.

Brewer, J. B., Zhao, Z., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. E. (1998). Making Memories: Brain Activity that Predicts How Well Visual Experience Will Be Remembered. *Science*, 281(5380), 1185–1187.

Broadbent, D. E. (1958). *Perception and communication*. New York, NY: Pergamon Press.

Brown, M. W., & Aggleton, J. P. (2001). Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nature Reviews Neuroscience*, 2(1), 51–61.

Brown, M. W., & Xiang, J. Z. (1998). Recognition memory: neuronal substrates of the judgement of prior occurrence. *Progress in neurobiology*, 55(2), 149–189.

Buckley, M. J., Booth, M. C., Rolls, E. T., & Gaffan, D. (2001). Selective perceptual impairments after perirhinal cortex ablation. *The Journal of Neuroscience*, 21(24), 9824–9836.

Buckley, M. J., & Gaffan, D. (2006). Perirhinal cortical contributions to object perception. *Trends in Cognitive Sciences*, 10(3), 100–107.

Buckner, R. L., Snyder, A. Z., Shannon, B. J., La Rossa, G., Sachs, R., Fotenos, A. F., Sheline, Y. I., et al. (2005). Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *The Journal of Neuroscience*, 25(34), 7709–7717.

Bunting, M. F., Conway, A. R. a., & Heitz, R. P. (2004). Individual differences in the fan effect and working memory capacity. *Journal of Memory and Language*, 51(4), 604–622.

Burgess, N., & Hitch, G. J. (2005). Computational models of working memory: putting long-term memory into context. *Trends in Cognitive Sciences*, 9(11), 535–541.

Burzynska, A. Z., Nagel, I. E., Preuschhof, C., Li, S.-C., Lindenberger, U., Bäckman, L., & Heekeren, H. R. (2011). Microstructure of Frontoparietal Connections Predicts Cortical Responsivity and Working Memory Performance. *Cerebral Cortex*, (10), 2261–2271.

Buschkuehl, M., & Jaeggi, S. M. (2010). Improving intelligence: a literature review. *Swiss Medical Weekly*, 140(19-20), 266–272.

Buschkuehl, M., Jaeggi, S. M., Hutchison, S., Perrig-Chiello, P., Dapp, C., Muller, M., Breil, F., et al. (2008). Impact of working memory training on memory performance in old-old adults. *Psychology and Aging*, 23(4), 743–753.

Buschkuehl, M., Jaeggi, S. M., & Jonides, J. (2012). Neuronal effects following working memory training. *Developmental Cognitive Neuroscience*, 2, 167–179.

Bussey, T. J., Saksida, L. M., & Murray, E. A. (2002). Perirhinal cortex resolves feature ambiguity in complex visual discriminations. *The European Journal of Neuroscience*, 15(2), 365–374.

Bussey, T. J., Saksida, L. M., & Murray, E. A. (2005). The perceptual-mnemonic/feature conjunction model of perirhinal cortex function. *The Quarterly Journal of Experimental Psychology*, 58(3-4), 269–282.

Cameron, A. S., & Archibald, Y. M. (1981). Verbal memory deficit after left fomix removal: a case report. *The International Journal of Neuroscience*, (12), 201–210.

Campo, P., Garrido, M. I., Moran, R. J., Maestú, F., García-Morales, I., Gil-Nagel, A., del Pozo, F., et al. (2012). Remote effects of hippocampal sclerosis on effective connectivity during working memory encoding: a case of connectional diaschisis? *Cerebral Cortex*, 22(6), 1225–1236.

Cansino, S., Maquet, P., Dolan, R. J., & Rugg, M. D. (2002). Brain activity underlying encoding and retrieval of source memory. *Cerebral Cortex*, 12(10), 1048–1056.

Carmel, P. W. (1985). Tumours of the third ventricle. *Acta Neurochirurgica*, 75(1-4), 136–146.

Carpenter, P. A., Just, M. A., & Shell, P. (1990). What one intelligence test measures: a theoretical account of the processing in the Raven Progressive Matrices Test. *Psychological Review*, 97(3), 404–431.

Carretti, B., Borella, E., & De Beni, R. (2007). Does strategic memory training improve the working memory performance of younger and older adults? *Experimental psychology*, 54(4), 311–320.

Catani, M., & Thiebaut de Schotten, M. (2008). A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex*, 44(8), 1105–1132.

Cavallini, E., Pagnin, A., & Vecchi, T. (2002). Aging and everyday memory: the beneficial effect of memory training. *Archives of gerontology and geriatrics*, 37(3), 241–257.

Cave, C. B., & Squire, L. R. (1992). Intact verbal and nonverbal short-term memory following damage to the human hippocampus. *Hippocampus*, 2(2), 151–163.

Charlton, R. A., Barrick, T. R., Markus, H. S., & Morris, R. G. (2009). The relationship between episodic long-term memory and white matter integrity in normal aging. *Neuropsychologia*, 48(1), 114–122.

Charlton, R. A., Schiavone, F., Barrick, T. R., Morris, R. G., & Markus, H. S. (2010). Diffusion tensor imaging detects age related white matter change over a 2 year follow-up which is associated with working memory decline. *Journal of Neurology, Neurosurgery, and Psychiatry*, 81(1), 13–19.

Chein, J. M., & Morrison, A. B. (2010). Expanding the mind's workspace: training and transfer effects with a complex working memory span task. *Psychonomic Bulletin & Review*, 17(2), 193–199.

Chen, S., Ross, T. J., Zhan, W., Myers, C. S., Chuang, K.-S., Heishman, S. J., Stein, E. A., et al. (2008). Group independent component analysis reveals consistent resting-state networks across multiple sessions. *Brain Research*, 1239, 141–151.

Chiang, M. C., Avedissian, C., Barysheva, M., Toga, A. W., McMahon, K. L., de Zubicaray, G. I., Wright, M. J., et al. (2009). Extending genetic linkage analysis to diffusion tensor images to map single gene effects on brain fiber architecture. *Medical Image Computing and Computer-Assisted Intervention*, 12(2), 506–513.

Choo, I. H., Lee, D. Y., Oh, J. S., Lee, J. S., Lee, D. S., Song, I. C., Youn, J. C., et al. (2010). Posterior cingulate cortex atrophy and regional cingulum disruption in mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging*, 31(5), 772–779.

Christiansen, J. C. (1971). Discussion of paper by K. Sugita et al. In W. Umbach (Ed.), *Special Topics in Stereotaxis: Epilepsy, Disorders of Behaviour, and Autonomic Balance* (p. 51). Stuttgart, Germany: Hippokrates.

Chua, E. F., Schacter, D. L., Rand-Giovannetti, E., & Sperling, R. A. (2007). Evidence for a Specific Role of the Anterior Hippocampal Region in Successful Associative Encoding. *Hippocampus*, 17, 1071–1080.

Cicerone, K. D., Langenbahn, D. M., Braden, C., Malec, J. F., Kalmar, K., Fraas, M., Felicetti, T., et al. (2011). Evidence-based cognitive rehabilitation: updated review of the literature from 2003 through 2008. *Archives of physical medicine and rehabilitation*, 92(4), 519–530.

Cipolotti, L., Bird, C. M., Good, T., Macmanus, D., Rudge, P., & Shallice, T. (2006). Recollection and familiarity in dense hippocampal amnesia: a case study. *Neuropsychologia*, 44(3), 489–506.

Cipolotti, L., Husain, M., Crinion, J., Bird, C. M., Khan, S. S., Losseff, N., Howard, R. S., et al. (2008). The role of the thalamus in amnesia: a tractography, high-resolution MRI and neuropsychological study. *Neuropsychologia*, 46(11), 2745–2758.

Cipolotti, L., & Maguire, E. A. (2003). A combined neuropsychological and neuroimaging study of topographical and non-verbal memory in semantic dementia. *Neuropsychologia*, 41(9), 1148–1159.

Clayton, N. S., & Dickinson, A. (1998). Episodic-like memory during cache recovery by scrub jays. *Nature*, 395(17), 4–6.

Colchester, A. C. F., Kingsley, D., Lasserson, D., Kendall, B., Bello, F., Rush, C., Stevens, T. G., et al. (2001). Structural MRI volumetric analysis in patients with organic amnesia, 1:

methods and comparative findings across diagnostic groups. *Journal of Neurology, Neurosurgery, and Psychiatry*, 71(1), 13–22.

Coleman, M. P., & Freeman, M. R. (2010). Wallerian degeneration, wld(s), and nmnat. *Annual review of neuroscience*, 33, 245–267.

Concha, L., Beaulieu, C., Collins, D. L., & Gross, D. W. (2009). White-matter diffusion abnormalities in temporal-lobe epilepsy with and without mesial temporal sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry*, 80(3), 312–319.

Concha, L., Beaulieu, C., & Gross, D. W. (2005). Bilateral limbic diffusion abnormalities in unilateral temporal lobe epilepsy. *Annals of Neurology*, 57(2), 188–196.

Conway, A. R., Jarrold, C., Kane, M. J., Miyake, A., & Towse, J. N. (2007). *Variation in Working Memory*. Oxford, UK: Oxford University Press.

Cordes, D., Haughton, V. M., Arfanakis, K., Wendt, G. J., Turski, P. a, Moritz, C. H., Quigley, M. a, et al. (2000). Mapping functionally related regions of brain with functional connectivity MR imaging. *American Journal of Neuroradiology*, 21(9), 1636–1644.

Corkin, S. (1968). Acquisition of motor skill after bilateral medial temporal-lobe excision. *Neuropsychologia*, 6(3), 255–265.

Corkin, S. (1984). Learning Consequences of Bilateral Medial Temporal Lobectomy: Clinical Course and Experimental Findings in H.M. *Seminars in Neurology*, 4(2), 249–259.

Corkin, S. (2002). What's new with the amnesic patient H.M.? *Nature Reviews Neuroscience*, 3(2), 153–160.

Corkin, S., Amaral, D. G., González, R. G., Johnson, K. A., & Hyman, B. T. (1997). H. M.'s medial temporal lobe lesion: findings from magnetic resonance imaging. *The Journal of Neuroscience*, 17(10), 3964–3979.

Courtney, S. M., Ungerleider, K. K., Keil, K., & Haxby, J. V. (1997). Transient and sustained activity in a distributed neural system for human working memory. *Nature*, 386, 608–611.

Craik, F. I. M. (2012). Levels of processing: past, present. and future? *Memory*, 10(5-6), 305–318.

Craik, F. I. M., & Lockhart, R. S. (1972). Levels of processing: A framework for memory research. *Journal of Verbal Learning and Verbal Behavior*, 11, 671–684.

Crawford, J. R., & Howell, D. C. (1998). Comparing an Individual's Test Score Against Norms Derived from Small Samples. *Clinical Neuropsychology*, 12, 482–486.

Dahlin, E., Neely, A. S., Larsson, A., Bäckman, L., Nyberg, L., & Backman, L. (2008). Transfer of learning after updating training mediated by the striatum. *Science*, 320(5882), 1510–1512.

Dahlin, E., Nyberg, L., Bäckman, L., & Neely, A. S. (2008). Plasticity of executive functioning in young and older adults: Immediate training gains, transfer, and long-term maintenance. *Psychology and Aging*, 23(4), 720–730.

Daitz, H. M. (1953). Note on the fibre content of the fornix system in man. *Brain*, 76(3), 509–512.

Daitz, H. M., & Powell, T. P. (1954). Studies of the connexions of the fornix system. *Journal of Neurology, Neurosurgery, and Psychiatry*, 17(1), 75–82.

Damoiseaux, J. S., Rombouts, S. A. R. B., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences of the United States of America*, 103(2), 13848–13853.

Damoiseaux, J. S., Smith, S. M., Witter, M. P., Sanz-Arigita, E. J., Barkhof, F., Scheltens, P., Stam, C. J., et al. (2009). White matter tract integrity in aging and Alzheimer's disease. *Human Brain Mapping*, 30(4), 1051–1059.

Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2006). Triple Dissociation in the Medial Temporal Lobes: Recollection, Familiarity, and Novelty. *Journal of Neurophysiology*, 96(4), 1902–1911.

Daselaar, S. M., Rombouts, S. A. R. B., Veltman, D. J., Raaijmakers, J. G., Lazeron, R. H., & Jonker, C. (2001). Parahippocampal activation during successful recognition of words: a self-paced event-related fMRI study. *NeuroImage*, 13, 1113–1120.

Davachi, L. (2006). Item, context and relational episodic encoding in humans. *Current opinion in Neurobiology*, 16(6), 693–700. 2

Davachi, L., & Goldman-Rakic, P. S. (2001). Primate rhinal cortex participates in both visual recognition and working memory tasks: functional mapping with 2-DG. *Journal of Neurophysiology*, 85(6), 2590–2601.

Davachi, L., Mitchell, J. P., & Wagner, A. D. (2003). Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. *Proceedings of the National Academy of Sciences of the United States of America*, 100(4), 2157–2162.

Davies, R. R., Graham, K. S., Xuereb, J. H., Williams, G. B., & Hodges, J. R. (2004). The human perirhinal cortex and semantic memory. *The European Journal of Neuroscience*, 20(9), 2441–2446.

De Luca, M., Beckmann, C. F., De Stefano, N., Matthews, P. M., & Smith, S. M. (2006). fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *NeuroImage*, 29(4), 1359–1367.

Del Vecchio, N., Liporace, J., Nei, M., Sperling, M., & Tracy, J. (2004). A dissociation between implicit and explicit verbal memory in left temporal lobe epilepsy. *Epilepsia*, 45(9), 1124–1133.

Della-Maggiore, V., Scholz, J. P., Johansen-Berg, H., & Paus, T. (2009). The rate of visuomotor adaptation correlates with cerebellar white-matter microstructure. *Human Brain Mapping*, 30(12), 4048–4053.

Denby, C. E., Vann, S. D., Tsivilis, D., Aggleton, J. P., Montaldi, D., Roberts, N., & Mayes, A. R. (2009). The frequency and extent of mammillary body atrophy associated with surgical removal of a colloid cyst. *American Journal of Neuroradiology*, 30(4), 736–743.

Di Paola, M., Caltagirone, C., Fadda, L., Sabatini, U., Serra, L., & Carlesimo, G. A. (2008). Hippocampal atrophy is the critical brain change in patients with hypoxic amnesia. *Hippocampus*, 18(7), 719–728.

Di Paola, M., Moscatelli, a, Bigler, E. D., Caltagirone, C., & Carlesimo, G. A. (2011). White matter changes in patients with hypoxic amnesia. *Neurocase*, 17(1), 46–56.

Diana, R. A., Yonelinas, A. P., & Ranganath, C. (2007). Imaging recollection and familiarity in the medial temporal lobe: a three-component model. *Trends in Cognitive Sciences*, 11(9), 379–386.

Diana, R. A., Yonelinas, A. P., & Ranganath, C. (2008). The effects of unitization on familiarity-based source memory: testing a behavioral prediction derived from neuroimaging data. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 34(4), 730–740.

Diana, R. A., Yonelinas, A. P., & Ranganath, C. (2009). Medial Temporal Lobe Activity during Source Retrieval Reflects Information Type, not Memory Strength. *Journal of Cognitive Neuroscience*, 22(8), 1–11.

Diehl, B., Busch, R. M., Duncan, J. S., Piao, Z., Tkach, J., & Lüders, H. O. (2008). Abnormalities in diffusion tensor imaging of the uncinate fasciculus relate to reduced memory in temporal lobe epilepsy. *Epilepsia*, 49(8), 1409–1418.

Dijkhuizen, R. M., van der Marel, K., Otte, W. M., Hoff, E. I., van der Zijden, J. P., van der Toorn, A., & van Meer, M. P. a. (2012). Functional MRI and Diffusion Tensor Imaging of Brain Reorganization After Experimental Stroke. *Translational Stroke Research*, 3(1), 36–43.

Dobbins, I. G., Foley, H., Schacter, D. L., & Wagner, A. D. (2002). Executive control during episodic retrieval: multiple prefrontal processes subserve source memory. *Neuron*, 35(5), 989–996.

Doeller, C. F., King, J. a, & Burgess, N. (2008). Parallel striatal and hippocampal systems for landmarks and boundaries in spatial memory. *Proceedings of the National Academy of Sciences of the United States of America*, 105(15), 5915–5920.

Dolan, R. J., & Fletcher, P. F. (1999). Encoding and retrieval in human medial temporal lobes: an empirical investigation using functional magnetic resonance imaging (fMRI). *Hippocampus*, 9(1), 25–34.

Donaldson, D. I., Petersen, S. E., Ollinger, J. M., & Buckner, R. L. (2001). Dissociating state and item components of recognition memory using fMRI. *NeuroImage*, 13(1), 129–142.

Du, A.T., Schuv, N., Amend, D., Laakso, M. P., Hsu, Y. Y., Jagust, W. J., Yave, K., et al. (2001). Magnetic resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer ' s disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 71, 441–447.

Duncan, J. S. (2006). EPS Mid-Career Award 2004: brain mechanisms of attention. *The Quarterly Journal of Experimental Psychology*, 59(1), 2–27.

Dörfel, D., Werner, A., Schaefer, M., von Kummer, R., & Karl, A. (2009). Distinct brain networks in recognition memory share a defined region in the precuneus. *The European Journal of Neuroscience*, 30(10), 1947–1959.

D'Esposito, M., Cooney, J. W., Gazzaley, A., Gibbs, S., & Postle, B. R. (2006). Is the prefrontal cortex necesssary for delay task performance? Evidence from lesion and fMRI data. *Journal of the International Neuropsychological Society*, 12, 248–260.

D'Esposito, M., Postle, B. R., Ballard, D., & Lease, J. (1999). Maintenance versus Manipulation of Information Held in Working Memory: An Event-Related fMRI Study. *Brain and Cognition*, 41(1), 66–86.

D'Esposito, M., Verfaellie, M., Alexander, M. P., & Katz, D. I. (1995). Amnesia following traumatic bilateral fornix transection. *Neurology*, 45(8), 1546–1550.

Eacott, M. J., Gaffan, D., & Murray, E. A. (1994). Preserved Recognition Memory for Small Sets, and Impaired Stimulus Identification for Large Sets, Following Rhinal Cortex Ablations in Monkeys. *The European Journal of Neuroscience*, 6, 1466–1478.

Ebeling, U., & Cramon, D. (1992). Topography of the Uncinate Fascicle and Adjacent Temporal Fiber Tracts. *Acta Neurochirurgica*, 115, 143–148.

Egan, J. P. (1975). *Signal detection theory and ROC analysis*. New York, NY: Academic Press.

Eichenbaum, H. (2004). Hippocampus: Cognitive processes and neural representations that underlie declarative memory. *Neuron*, 44(1), 109–120.

Eichenbaum, H., Yonelinas, A. P., & Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annual Review of Neuroscience*, 30, 123–152.

Eldridge, L. L., Engel, S. A., Zeineh, M. M., Bookheimer, S. Y., & Knowlton, B. J. (2005). A dissociation of encoding and retrieval processes in the human hippocampus. *The Journal of Neuroscience*, 25(13), 3280–3286.

Epstein, R. A. (2008). Parahippocampal and retrosplenial contributions to human spatial navigation. *Trends in Cognitive Sciences*, 12(10), 388–396.

Epstein, R. A., & Kanwisher, N. (1998). A cortical representation the local visual environment. *Nature*, 392(6676), 598–601.

Erickson, K. I., Colcombe, S. J., Wadhwa, R., Bherer, L., Peterson, M. S., Scalf, P. E., Kim, J. S., et al. (2007). Training-induced functional activation changes in dual-task processing: an FMRI study. *Cerebral Cortex*, 17(1), 192–204.

Esposito, F., Bertolino, A., Scarabino, T., Latorre, V., Blasi, G., Popolizio, T., Tedeschi, G., et al. (2006). Independent component model of the default-mode brain function: Assessing the impact of active thinking. *Brain Research Bulletin*, 70(4-6), 263–269.

Ezzyat, Y., & Olson, I. R. (2008). The medial temporal lobe and visual working memory: comparisons across tasks, delays, and visual similarity. *Cognitive, Affective, & Behavioral Neuroscience*, 8(1), 32–40.

Farovik, A., Dupont, L. M., Arce, M., & Eichenbaum, H. (2008). Medial prefrontal cortex supports recollection, but not familiarity, in the rat. *The Journal of Neuroscience*, 28(50), 13428–13434.

Feigenbaum, J. D., & Morris, R. G. (2004). Allocentric versus egocentric spatial memory after unilateral temporal lobectomy in humans. *Neuropsychology*, 18(3), 462–472.

Fellgiebel, A., Schermuly, I., Gerhard, A., Keller, I., Albrecht, J., Weibrich, C., Müller, M. J., et al. (2008). Functional relevant loss of long association fibre tracts integrity in early Alzheimer's disease. *Neuropsychologia*, 46(6), 1698–1706.

Fellgiebel, A., Wille, P., Müller, M. J., Winterer, G., Scheurich, A., Vucurevic, G., Schmidt, L. G., et al. (2004). Ultrastructural hippocampal and white matter alterations in mild cognitive impairment: a diffusion tensor imaging study. *Dementia and Geriatric Cognitive Disorders*, 18(1), 101–108.

Fellgiebel, A., & Yakushev, I. (2011). Diffusion tensor imaging of the hippocampus in MCI and early Alzheimer's disease. *Journal of Alzheimer's disease*, 26(3), 257–262.

Fields, R. D. (2008). White matter in learning, cognition and psychiatric disorders. *Trends in Neurosciences*, 31(7), 361–370.

Filippini, N., MacIntosh, B. J., Hough, M. G., Goodwin, G. M., Frisoni, G. B., Smith, S. M., Matthews, P. M., et al. (2009). Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. *Proceedings of the National Academy of Sciences of the United States of America*, 106(17), 7209–7214.

Fletcher, P. C., & Henson, R. N. (2001). Frontal lobes and human memory: Insights from functional neuroimaging. *Brain*, 124(5), 849–881.

Flöel, A., de Vries, M. H., Scholz, J. P., Breitenstein, C., & Johansen-Berg, H. (2009). White matter integrity in the vicinity of Broca's area predicts grammar learning success. *NeuroImage*, 47(4), 1974–1981.

Fornito, A., Harrison, B. J., Zalesky, A., & Simons, J. S. (2012). Competitive and cooperative dynamics of large-scale brain functional networks supporting recollection. *Proceedings of the National Academy of Sciences of the United States of America*, 109(31), 12788–12793.

Fortin, N. J., Wright, S. P., & Eichenbaum, H. (2004). Recollection-like memory retrieval in rats is dependent on the hippocampus. *Nature*, 431(7005), 188–191.

Fox, M. D., & Greicius, M. D. (2010). Clinical applications of resting state functional connectivity. *Frontiers in Systems Neuroscience*, 4(19), 1–13.

Fransson, P., Skiöld, B., Horsch, S., Nordell, A., Blennow, M., Lagercrantz, H., & Aden, U. (2007). Resting-state networks in the infant brain. *Proceedings of the National Academy of Sciences of the United States of America*, 104(39), 15531–15536.

Frisoni, G. B., Testa, C., Zorzan, A., Sabattoli, F., Beltramello, A., Soininen, H., & Laakso, M. P. (2002). Detection of grey matter loss in mild Alzheimer's disease with voxel based morphometry. *Journal of Neurology, Neurosurgery, and Psychiatry*, 73, 657–665.

Fuentemilla, L., Camara, E., Munte, T. F., Kramer, U. M., Cunillera, T., Marco-Pallares, J., Tempelmann, C., et al. (2009). Individual Differences in True and False Memory Retrieval Are Related to White Matter Brain Microstructure. *The Journal of Neuroscience*, 29(27), 8698–8703.

Fujie, S., Namiki, C., Nishi, H., Yamada, M., Miyata, J., Sakata, D., Sawamoto, N., et al. (2008). The role of the uncinate fasciculus in memory and emotional recognition in amnestic mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders*, 26(5), 432–439.

Fuster, J. M. (1997). Network memory. *Trends in Neurosciences*, 20(10), 451–459.

Gaffan, D. (1972). Loss of recognition memory in rats with lesions of the fornix. *Neuropsychologia*, 10(3), 327–341.

Gaffan, D. (2001). What is a memory system? Horel's critique revisited. *Behavioural Brain Research*, 127(1), 5–11.

Gaffan, D. (2002). Against memory systems. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 357(1424), 1111–1121.

Gaffan, D., & Gaffan, E. A. (1991). Amnesia in man following transection of the fornix. A review. *Brain*, 114(6), 2611–2618.

Gaffan, D., & Harrison, S. (1984). Reversal learning by fornix-transected monkeys. *The Quarterly Journal of Experimental Psychology*, 36(3), 223–234.

Gaffan, D., & Harrison, S. (1989a). Place memory and scene memory: effects of fornix transection in the monkey. *Experimental Brain Research*, 74, 202–212.

Gaffan, D., & Harrison, S. (1989b). A comparison of the effects of fornix transection and sulcus principalis ablation upon spatial learning by monkeys. *Behavioural Brain Research*, 31(3), 207–220.

Gaffan, E. A., Gaffan, D., & Hodges, J. R. (1991). Amnesia following damage to the left fornix and to other sites. *Brain*, 114, 1297–1313.

Garcia-Bengochea, F., & Friedman, W. A. (1987). Persistent memory loss following section of the anterior fornix in humans. A historical review. *Surgical Neurology*, 27(4), 361–364.

Gardiner, J. M. (1988). Functional aspects of recollective experience. *Memory & Cognition*, 16(4), 309–313.

Gardiner, J. M., & Richardson-Klavehn, A. (2000). Remembering and Knowing. In E. Tulving & F. I. M. Craik (Eds.), *The Oxford Handbook of Memory* (pp. 229–244). New York, NY: Oxford University Press.

Gauthier, I., & Tarr, M. J. (1997). Becoming a “Greeble” expert: exploring mechanisms for face recognition. *Vision research*, 37(12), 1673–1682.

Gershberg, F. B., & Shimamura, A. P. (1995). Impaired use of organizational strategies in free recall following frontal lobe damage. *Neuropsychologia*, 13, 1305–1333.

Glanzer, M., & Cunitz, A. R. (1966). Storage mechanisms in free recall. *Journal of Verbal Learning and Verbal Behavior*, 5, 351–360.

Glanzer, M., Hilford, A., Kim, K., & Adams, J. K. (1999). Further tests of dual-process theory: A reply to Yonelinas (1999). *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 25(2), 522–523.

Gold, J. J., Smith, C. N., Bayley, P. J., Shrager, Y., Brewer, J. B., Stark, C. E. L., Hopkins, R. O., et al. (2006). Item memory, source memory, and the medial temporal lobe: concordant findings from fMRI and memory-impaired patients. *Proceedings of the National Academy of Sciences of the United States of America*, 103(24), 9351–9356.

Gold, J. J., & Squire, L. R. (2005). Quantifying medial temporal lobe damage in memory-impaired patients. *Hippocampus*, 15(1), 79–85.

Goldstein, F. C., Mao, H., Wang, L., Ni, C., Lah, J. J., & Levey, A. I. (2009). White Matter Integrity and Episodic Memory Performance in Mild Cognitive Impairment: A Diffusion Tensor Imaging Study. *Brain Imaging and Behavior*, 3(2), 132–141.

Gonsalves, B. D., Kahn, I., Curran, T., Norman, K. A., & Wagner, A. D. (2005). Memory strength and repetition suppression: multimodal imaging of medial temporal cortical contributions to recognition. *Neuron*, 47(5), 751–761.

Grady, C. L., Haxby, J. V, Horwitz, B., Sundaram, M., Berg, G., Schapiro, M., Friedland, R., et al. (1988). Longitudinal study of the early neuropsychological and cerebral metabolic

changes in dementia of the Alzheimer type. *Journal of Clinical and Experimental Neuropsychology*, 10(5), 576–596.

Graf, P., & Schacter, D. L. (1985). Implicit and Explicit Memory for New Associations in Normal and Amnesic Subjects. *Journal of Experimental Psychology: Learning, Memory, and Cognition.*, 11(2), 501–518.

Graham, K. S., Barense, M. D., & Lee, A. C. H. (2010). Going beyond LTM in the MTL: a synthesis of neuropsychological and neuroimaging findings on the role of the medial temporal lobe in memory and perception. *Neuropsychologia*, 48(4), 831–853.

Graham, K. S., Simons, J. S., Pratt, K. H., Patterson, K., & Hodges, J. R. (2000). Insights from semantic dementia on the relationship between episodic and semantic memory. *Neuropsychologia*, 38(3), 313–324.

Gray, J. R., Chabris, C. F., & Braver, T. S. (2003). Neural mechanisms of general fluid intelligence. *Nature Neuroscience*, 6(3), 316–322.

Greicius, M. D., Kiviniemi, V., Tervonen, O., Vainionpää, V., Alahuhta, S., Reiss, A. L., & Menon, V. (2008). Persistent default-mode network connectivity during light sedation. *Human Brain Mapping*, 29(7), 839–847.

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America*, 100(1), 253–258.

Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer ' s disease from healthy aging : Evidence from functional MRI. *Proceedings of the National Academy of Sciences of the United States of America*, 101(13), 4637–4642.

Greve, D. N., & Fischl, B. (2009). Accurate and robust brain image alignment using boundary-based registration. *NeuroImage*, 48(1), 63–72.

Grober, E., & Buschke, H. (1987). Genuine memory deficits in dementia. *Developmental Neuropsychology*, 3, 13–36.

Halford, G. S., Cowan, N., & Andrews, G. (2007). Separating Cognitive Capacity from Knowledge: A New Hypothesis. *Trends in Cognitive Sciences*, 11(6), 236–242.

Hampson, M., Driesen, N. R., Skudlarski, P., Gore, J. C., & Constable, R. T. (2006). Brain connectivity related to working memory performance. *The Journal of Neuroscience*, 26(51), 13338–13343.

Hampstead, B. M., Sathian, K., Phillips, P. A., Amaraneni, A., Delaune, W. R., & Stringer, A. Y. (2012). Mnemonic Strategy Training Improves Memory for Object Location Associations in Both Healthy Elderly and Patients With Amnestic Mild Cognitive impairment: A Randomized, Single-Blind Study. *Neuropsychology*, 26(3), 385–399.

Hampton, R. R., Hampstead, B. M., & Murray, E. A. (2004). Selective hippocampal damage in rhesus monkeys impairs spatial memory in an open-field test. *Hippocampus*, 14(7), 808–818.

Hannula, D. E., & Ranganath, C. (2008). Medial temporal lobe activity predicts successful relational memory binding. *The Journal of Neuroscience*, 28(1), 116–124.

Hannula, D. E., Tranel, D., & Cohen, N. J. (2006). The long and the short of it: relational memory impairments in amnesia, even at short lags. *The Journal of Neuroscience*, 26(32), 8352–8359.

Hartley, T., Bird, C. M., Chan, D., Cipolotti, L., Husain, M., Vargha-Khadem, F., & Burggren, A. C. (2007). The Hippocampus is Required for Short-Term Topographical Memory in Humans. *Hippocampus*, 48, 34–48.

Haskins, L. A., Yonelinas, A. P., Quamme, J. R., & Ranganath, C. (2008). Perirhinal cortex supports encoding and familiarity-based recognition of novel associations. *Neuron*, 59(4), 554–560.

Hattori, T., Sato, R., Aoki, S., Yuasa, T., & Mizusawa, H. (2012). Different patterns of fornix damage in idiopathic normal pressure hydrocephalus and Alzheimer disease. *American Journal of Neuroradiology*, 33(2), 274–279.

Heindel, C., Salmon, D. P., Shults, W., Walicke, A., & Butters, N. (1989). Neuropsychological Evidence for Multiple Implicit Memory Systems: A Comparison of Alzheimer's, Huntington's, and Parkinson's Disease Patients. *The Journal of Neuroscience*, 9(2), 582–587.

Henson, R. N., Cansino, S., Herron, J. E., Robb, W. G. K., & Rugg, M. D. (2003). A familiarity signal in human anterior medial temporal cortex? *Hippocampus*, 13(2), 301–304.

Henson, R. N., Rugg, M. D., Shallice, T., Josephs, O., & Dolan, R. J. (1999). Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. *The Journal of Neuroscience*, 19(10), 3962–3972.

Hitch, G. J., & Logie, R. H. (1996). Working memory (Special Issue). *The Quarterly Journal of Experimental Psychology*, *49A*, 1–266.

Hodges, J. R., & Carpenter, K. (1991). Anterograde amnesia with fornix damage following removal of 3rd ventricle colloid cyst. *Journal of Neurology, Neurosurgery, and Psychiatry*, 54(7), 633–638.

Holdstock, J. S., Gutnikov, S. A., Gaffan, D., & Mayes, A. R. (2000). Perceptual and mnemonic matching-to-sample in humans: contributions of the hippocampus, perirhinal and other medial temporal lobe cortices. *Cortex*, 36(3), 301–322.

Holdstock, J. S., Mayes, A. R., Gong, Q. Y., Roberts, N., & Kapur, N. (2005). Item recognition is less impaired than recall and associative recognition in a patient with selective hippocampal damage. *Hippocampus*, 15(2), 203–215.

Holdstock, J. S., Mayes, A. R., Roberts, N., Cezayirli, E., Isaac, C. L., O'Reilly, R. C., & Norman, K. A. (2002). Under what conditions is recognition spared relative to recall after selective hippocampal damage in humans? *Hippocampus*, 12(3), 341–351.

Holdstock, J. S., Parslow, D. M., Morris, R. G., Fleminger, S., Abrahams, S., Denby, C. E., Montaldi, D., et al. (2008). Two case studies illustrating how relatively selective hippocampal lesions in humans can have quite different effects on memory. *Hippocampus*, 18(7), 679–691.

Holdstock, J. S., Shaw, C., & Aggleton, J. P. (1995). The performance of amnesic subjects on tests of delayed mathing-to-sample and delayed mathing-to-position. *Science*, 33(12), 1583–1596.

Holmes, J., Gathercole, S. E., & Dunning, D. L. (2009). Adaptive training leads to sustained enhancement of poor working memory in children. *Developmental Science*, 12(4), 9–15.

Hossiep, R., Turck, D., & Hasella, M. (1999). *Bochmumer Matrizentest : BOMAT- Advanced short version*. Gottingen, Germany: Hogrefe.

Huang, H., Fan, X., Weiner, M., Martin-Cook, K., Xiao, G., Davis, J., Devous, M., et al. (2012). Distinctive disruption patterns of white matter tracts in Alzheimer's disease with full diffusion tensor characterization. *Neurobiology of Aging*, 33(9), 2029–2045.

Hugg, J. W., Butterworth, E. J., & Kuzniecky, R. I. (1999). Diffusion mapping applied to mesial temporal lobe epilepsy: Preliminary observations. *Neurology*, 53(1), 173–173.

Iaria, G., Petrides, M., Dagher, A., Pike, B., & Bohbot, V. D. (2003). Cognitive strategies dependent on the hippocampus and caudate nucleus in human navigation: variability and change with practice. *The Journal of Neuroscience*, 23(13), 5945–5952.

Jack, C. R., Petersen, R. C., Xu, Y. C., O'Brien, P. C., Smith, G. E., Ivnik, R. J., Boeve, B. F., et al. (1999). Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology*, 52(7), 1397–1403.

Jacoby, L. L. (1991). A Process Dissociation Framework : Separating Intentional Uses of Memory Automatic from Intetional Uses of Memory. *Journal of Memory and Language*, 30, 513–541.

Jaeggi, S. M., Buschkuehl, M., Jonides, J., & Perrig, W. J. (2008). Improving fluid intelligence with training on working memory. *Proceedings of the National Academy of Sciences of the United States of America*, 105(19), 6829–6833.

Jaeggi, S. M., Buschkuehl, M., Jonides, J., & Shah, P. (2011). Short- and long-term benefits of cognitive training. *Proceedings of the National Academy of Sciences of the United States of America*, 108(25), 10081–10086.

James, W. (1890). *The Principles of Psychology*. New York, NY: Holt.

Jeneson, A., & Squire, L. R. (2012). Working memory, long-term memory, and medial temporal lobe function. *Learning & memory*, 19(1), 15–25.

Jobe, J. B., Smith, D. M., Ball, K., Tennstedt, S. L., Marsiske, M., Willis, S. L., Rebok, G. W., et al. (2001). ACTIVE: a cognitive intervention trial to promote independence in older adults. *Controlled clinical trials*, 22(4), 453–479.

Johansen-Berg, H. (2010). Behavioural relevance of variation in white matter microstructure. *Current Opinion in Neurobiology*, 23(4), 351–358.

Johansen-Berg, H., & Behrens, T. E. J. (2006). Just pretty pictures? What diffusion tractography can add in clinical neuroscience. *Current Opinion in Neurology*, 19(4), 379–385.

Jones, D. K., & Cercignani, M. (2010). Twenty-five pitfalls in the analysis of diffusion MRI data. *NMR in biomedicine*, 23(7), 803–820.

Jonides, J. (2004). How does practice makes perfect? *Nature Neuroscience*, 7(1), 10–11.

Jäger, A. O., Süß, H. M., & Beauducel, A. (1997). *Berlin Test of Intelligence Structure, BIS-Test, Form 4*. Gottingen, Germany: Hogrefe.

Kannurpatti, S. S., Biswal, B. B., Kim, Y. R., & Rosen, B. R. (2008). Spatio-temporal characteristics of low-frequency BOLD signal fluctuations in isoflurane-anesthetized rat brain. *NeuroImage*, 40, 1738–1747.

Kanwisher, N., Mcdermott, J., & Chun, M. M. (1997). The Fusiform Face Area : A Module in Human Extrastriate Cortex Specialized for Face Perception. *The Journal of Neuroscience*, 17(11), 4302–4311.

Keller, T. A., & Just, M. A. (2009). Altering cortical connectivity: remediation-induced changes in the white matter of poor readers. *Neuron*, 64(5), 624–631.

Kelly, C., Foxe, J. J., & Garavan, H. (2006). Patterns of normal human brain plasticity after practice and their implications for neurorehabilitation. *Archives of physical medicine and rehabilitation*, 87(2), 20–29.

Kim, M. J., & Whalen, P. J. (2009). The Structural Integrity of an Amygdala-Prefrontal Pathway Predicts Trait Anxiety. *The Journal of Neuroscience*, 29(37), 11614–11618.

Kim, S., Jeneson, A., van der Horst, A. S., Frascino, J. C., Hopkins, R. O., & Squire, L. R. (2011). Memory, visual discrimination performance, and the human hippocampus. *The Journal of Neuroscience*, 31(7), 2624–2629.

King, J. a, Trinkler, I., Hartley, T., Vargha-Khadem, F., & Burgess, N. (2004). The hippocampal role in spatial memory and the familiarity--recollection distinction: a case study. *Neuropsychology*, 18(3), 405–417.

Kirwan, C. B., Wixted, J. T., & Squire, L. R. (2008). Activity in the medial temporal lobe predicts memory strength, whereas activity in the prefrontal cortex predicts recollection. *The Journal of Neuroscience*, 28(42), 10541–10548.

Kirwan, C. B., Wixted, J. T., & Squire, L. R. (2010). A demonstration that the hippocampus supports both recollection and familiarity. *Proceedings of the National Academy of Sciences of the United States of America*, 107(1), 344–348.

Klingberg, T. (2010). Training and plasticity of working memory. *Trends in Cognitive Sciences*, 14(7), 317–324.

Klingberg, T., Fernell, E., Olesen, P. J., Johnson, M., Gustafsson, P., Dahlström, K., Gillberg, C. G., et al. (2005). Computerized Training of Working Memory in Children With ADHD-A Randomized, Controlled Trial. *Journal of the American Academy of Child & Adolescent Psychiatry*, 44(2), 177–186.

Klunk, W. E., Engler, H., Nordberg, A., Wang, Y., Blomqvist, G., Holt, D. P., Bergstro, M., et al. (2004). Imaging Brain Amyloid in Alzheimer ' s Disease with Pittsburgh Compound-B. *Annals of Neurology*, 55, 306–319.

Knowlton, B. J., & Squire, L. R. (1995). Remembering and knowing: two different expressions of declarative memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition.*, 21(3), 699–710.

Knutson, A. R., Hopkins, R. O., & Squire, L. R. (2012). Visual discrimination performance, memory, and medial temporal lobe function. *Proceedings of the National Academy of Sciences of the United States of America*, 109(32), 13106–13111.

Kopelman, M. D., Bright, P., Buckman, J., Fradera, A., Yoshimasu, H., Jacobson, C., & Colchester, A. C. F. (2007). Recall and recognition memory in amnesia: patients with hippocampal, medial temporal, temporal lobe or frontal pathology. *Neuropsychologia*, 45(6), 1232–1246.

Köhler, S., Crane, J., & Milner, B. (2002). Differential contributions of the parahippocampal place area and the anterior hippocampus to human memory for scenes. *Hippocampus*, 12(6), 718–723.

Lashley, K. S. (1950). In Search of Engram. *Society for Experimental Biology. Symposium No.4: Physiological mechamisms in animal behaviour* (pp. 452–482). Cambridge, UK: University Press.

Le Bihan, D. (1995). *Diffusion and Perfusion Magnetic Resonance Imaging. Applications to Functional MRI*. New York, NY: Raven Press.

Le Bihan, D., & Breton, E. (1985). Imagerie de diffusion in-vivo par résonance magnétique nucléaire. *Comptes rendus de l'Académie des sciences*, 301(15), 1109–1112.

Le Bihan, D., Mangin, J. F., Poupon, C., Clark, C., Pappata, S., Molko, N., & Chabriat, H. (2001). Diffusion tensor imaging: concepts and applications. *Journal of Magnetic Resonance Imaging*, 13(4), 534–46.

Lee, A. C. H., Bandelow, S., Schwarzbauer, C., Henson, R. N., & Graham, K. S. (2006). Perirhinal cortex activity during visual object discrimination: an event-related fMRI study. *NeuroImage*, 33(1), 362–373.

Lee, A. C. H., Barense, M. D., & Graham, K. S. (2005). The contribution of the human medial temporal lobe to perception: bridging the gap between animal and human studies. *The Quarterly Journal of Experimental Psychology*, 58(3-4), 300–325.

Lee, A. C. H., Brodersen, K., & Rudebeck, S. R. (2012). Disentangling spatial perception and spatial memory in the hippocampus: a univariate and multivariate pattern analysis fMRI study. *Journal of Cognitive Neuroscience*.

Lee, A. C. H., Buckley, M. J., Gaffan, D., Emery, T., Hodges, J. R., & Graham, K. S. (2006). Differentiating the roles of the hippocampus and perirhinal cortex in processes beyond long-term declarative memory: a double dissociation in dementia. *The Journal of Neuroscience*, 26(19), 5198–5203.

Lee, A. C. H., Buckley, M. J., Pegman, S. J., Spiers, H. J., Scahill, V. L., Gaffan, D., Bussey, T. J., et al. (2005). Specialization in the medial temporal lobe for processing of objects and scenes. *Hippocampus*, 15(6), 782–797.

Lee, A. C. H., Bussey, T. J., Murray, E. A., Saksida, L. M., Epstein, R. A., Kapur, N., Hodges, J. R., et al. (2005). Perceptual deficits in amnesia: challenging the medial temporal lobe "mnemonic" view. *Neuropsychologia*, 43(1), 1–11.

Lee, A. C. H., & Rudebeck, S. R. (2010a). Investigating the interaction between spatial perception and working memory in the human medial temporal lobe. *Journal of Cognitive Neuroscience*, 22(12), 2823–2835.

Lee, A. C. H., & Rudebeck, S. R. (2010b). Human medial temporal lobe damage can disrupt the perception of single objects. *The Journal of Neuroscience*, 30(19), 6588–6594.

Lee, A. C. H., Scahill, V. L., & Graham, K. S. (2008). Activating the medial temporal lobe during oddity judgment for faces and scenes. *Cerebral Cortex*, 18(3), 683–696.

Lee, A. C. H., Yeung, L.-K., & Barense, M. D. (2012). The hippocampus and visual perception. *Frontiers in Human Neuroscience*, 6, 1–17.

Lever, C., Wills, T., Cacucci, F., Burgess, N., & O'Keefe, J. (2002). Long-term plasticity in hippocampal place-cell representation of environmental geometry. *Nature*, 416(6876), 90–94.

Levy, D. A., Shrager, Y., & Squire, L. R. (2005). Intact visual discrimination of complex and feature-ambiguous stimuli in the absence of perirhinal cortex. *Learning & Memory*, 61–66.

Li, S.-C., Schmiedek, F., Huxhold, O., Röcke, C., Smith, J., & Lindenberger, U. (2008). Working memory plasticity in old age: practice gain, transfer, and maintenance. *Psychology and Aging*, 23(4), 731–742.

Litman, L., Awipi, T., & Davachi, L. (2010). Category-specificity in the Human Medial Temporal Lobe Cortex. *Hippocampus*, 19(3), 308–319.

Londoño, A., Castillo, M., Lee, Y. Z., & Smith, J. K. (2003). Apparent diffusion coefficient measurements in the hippocampi in patients with temporal lobe seizures. *American Journal of Neuroradiology*, 24(8), 1582–1586.

Loosli, S. V, Buschkuehl, M., Perrig, W. J., & Jaeggi, S. M. (2011). Working memory training improves reading processes in typically developing children. *Child Neuropsychology*, 1–17.

Lowe, M. J., Mock, B. J., & Sorenson, J. A. (1998). Functional Connectivity in Single and Multislice Echoplanar Imaging Using Resting-State Fluctuations. *Neuroimage*, 132(7), 119–132.

Macmillan, N. A., & Creelman, C. D. (2005). *Detection Theory: A User's Guide* (2nd ed.). Mahwah, NJ: Lawrence Erlbaum Associates, Inc.

Maguire, E. A., Burggren, A. C., Donnett, J. G., Frackowiak, R. S. J., Frith, C. D., & O'Keefe, J. (1998). Knowing where and getting there: a human navigation network. *Science*, 280(5365), 921–924.

Maguire, E. A., Frackowiak, R. S. J., & Frith, C. D. (1997). Recalling routes around london: activation of the right hippocampus in taxi drivers. *The Journal of Neuroscience*, 17(18), 7103–7110.

Maguire, E. A., Gadian, D. G., Johnsrude, I. S., Good, C. D., Ashburner, J., Frackowiak, R. S. J., & Frith, C. D. (2000). Navigation-related structural change in the hippocampi of taxi drivers. *Proceedings of the National Academy of Sciences of the United States of America*, 97(8), 4398–4403.

Maguire, E. A., Nannery, R., & Spiers, H. J. (2006). Navigation around London by a taxi driver with bilateral hippocampal lesions. *Brain*, 129, 2894–2907.

Maguire, E. A., Spiers, H. J., Good, C. D., Hartley, T., Frackowiak, R. S. J., & Burgess, N. (2003). Navigation expertise and the human hippocampus: a structural brain imaging analysis. *Hippocampus*, 13(2), 250–259.

Maguire, E. A., Vargha-Khadem, F., & Mishkin, M. (2001). The effects of bilateral hippocampal damage on fMRI regional activations and interactions during memory retrieval. *Brain*, 124(Pt 6), 1156–1170.

Maguire, E. A., Woollett, K., & Spiers, H. J. (2006). London Taxi Drivers and Bus Drivers : A Structural MRI and Neuropsychological Analysis. *Hippocampus*, 16, 1091–1101.

Mahut, H. (1971). Spatial and object reversal learning in monkeys with partial temporal lobe ablations. *Neuropsychologia*, 9(4), 409–424.

Mahut, H. (1972). A selective spatial deficit in monkeys after transection of the fornix. *Neuropsychologia*, 10(1), 65–74.

Malach, R., Reppas, J. B., Benson, R. R., Kwong, K. K., Jlang, H., Kennedy, W. A., Ledden, P. J., et al. (1995). Object-related activity revealed by functional magnetic resonance imaging in human occipital cortex. *Proceedings of the National Academy of Sciences of the United States of America*, 92, 8135–8139.

Mandler, G. (1980). Recognizing: The judgment of previous occurrence. *Psychological Review*, 87, 252–271.

Mandler, G., & Boeck, W. J. (1974). Retrieval processes in recognition. *Memory & Cognition*, 2(4), 613–615.

Manns, J. R., Hopkins, R. O., Reed, J. M., Kitchener, E. G., & Squire, L. R. (2003). Recognition memory and the human hippocampus. *Neuron*, 37(1), 171–180.

Manns, J. R., & Squire, L. R. (1999). Impaired Recognition Memory on the Doors and and People Test After Damage Limited to the Hippocampal Region. *Hippocampus*, 499(5), 495–499.

Markowska, A. L., Olton, D. S., Murray, E. A., & Gaffan, D. (1989). A comparative analysis of the role of fornix and cingulate cortex in memory: rats. *Experimental Brain Research*, 74(1), 187–201.

Mayes, A. R., Holdstock, J. S., Isaac, C. L., Hunkin, N. M., & Roberts, N. (2002). Relative sparing of item recognition memory in a patient with adult-onset damage limited to the hippocampus. *Hippocampus*, 12(3), 325–340.

Mayes, A. R., Holdstock, J. S., Isaac, C. L., Montaldi, D., Grigor, J., Gummer, A., Cariga, P., et al. (2004). Associative recognition in a patient with selective hippocampal lesions and relatively normal item recognition. *Hippocampus*, 14(6), 763–784.

Mayes, A. R., Montaldi, D., & Migo, E. (2007). Associative memory and the medial temporal lobes. *Trends in Cognitive Sciences*, 11(3), 126–135.

McCarthy, R. a, Kopelman, M. D., & Warrington, E. K. (2005). Remembering and forgetting of semantic knowledge in amnesia: a 16-year follow-up investigation of RFR. *Neuropsychologia*, 43(3), 356–372.

McCormick, C., Moscovitch, M., Protzner, a B., Huber, C. G., & McAndrews, M. P. (2010). Hippocampal-neocortical networks differ during encoding and retrieval of relational memory: functional and effective connectivity analyses. *Neuropsychologia*, 48(11), 3272–3281.

McKeown, M., Hansen, L. K., & Sejnowski, T. J. (2003). Independent component analysis of functional MRI: what is signal and what is noise? *Current Opinion in Neurobiology*, 13(5), 620–629.

McMackin, D., Cockburn, J., Anslow, P., & Gaffan, D. (1995). Correlation of Fornix Damage with Memory Impairment in Six Cases of Colloid Cyst Removal. *Acta Neurochirurgica*, 135(135), 12–18.

McNamara, D. S., & Scott, J. L. (2001). Working memory capacity and strategy use. *Memory & Cognition*, 29(1), 10–7.

Medina, D., DeToledo-Morrell, L., Urresta, F., Gabrieli, J. D. E., Moseley, M., Fleischman, D., Bennett, D. A., et al. (2006). White matter changes in mild cognitive impairment and AD: A diffusion tensor imaging study. *Neurobiology of Aging*, 27(5), 663–672.

Metzler-Baddeley, C., Jones, D. K., Belaroussi, B., Aggleton, J. P., & O'Sullivan, M. J. (2011). Frontotemporal connections in episodic memory and aging: a diffusion MRI tractography study. *The Journal of Neuroscience*, 31(37), 13236–13245.

Meunier, M., Bachevalier, J., Mishkin, M., & Murray, E. A. (1993). Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. *The Journal of Neuroscience*, 13(12), 5418–5432.

Meyers, K. R., & Meyers, J. E. (1995). *Rey Complex Figure Test and Recognition Trial (RCFT)*. Odessa, FL: Psychological Assesment Resources.

Miller, G. A. (1956). The magical number seven, plus or minus two: Some limits on our capacity for processing information. *Psychological Review*, 63, 81–97.

Milner, B. (1971). Interhemispheric differences in the localization of psychological processes in man. *British Medical Bulletin*, 27(3), 272–277.

Milner, B. (1972). Disorders in learning and memory after temporal lobe lesions in man. *Clinical Neurosurgery*, 3, 421–446.

Milner, B. (2005). The medial temporal-lobe amnesic syndrome. *The Psychiatric Clinics of North America*, 28(3), 599–611.

Milner, B., Corkin, S., & Teuber, H.-L. (1968). Further analysis of the hippocampal amnesic syndrome: 14-year follow-up study of H.M. *Neuropsychologia*, 6(3), 215–234.

Mioshi, E., Dawson, K., Mitchell, J. P., Arnold, R., & Hodges, J. R. (2006). The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *International Journal of Geriatric Psychiatry*, 21(11), 1078–1085.

Mishkin, M. (1978). Memory in monkeys severly impaired by combined but not by separate removal of amygdala and hippocampus. *Nature*, 273, 297–298.

Mishkin, M., Suzuki, W. A., Gadian, D. G., & Vargha-Khadem, F. (1997). Hierarchical organization of cognitive memory. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 352(1360), 1461–1467.

Miyake, A., & Shah, P. (1999). *Models of working memory: mechanisms of active maintenance and executive control*. New York, NY: Cambridge University Press.

Montaldi, D., & Mayes, A. R. (2010). The role of recollection and familiarity in the functional differentiation of the medial temporal lobes. *Hippocampus*, 20(11), 1291–1314.

Montaldi, D., Spencer, T. J., Roberts, N., & Mayes, A. R. (2006). The neural system that mediates familiarity memory. *Hippocampus*, 16(5), 504–520.

Moody, D. E. (2009). Can intelligence be increased by training on a task of working memory? *Intelligence*, 37(4), 327–328.

Morris, R. G., Garrud, P., Rawlins, J. N. P., & O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature*, 297, 681–682.

Morrison, A., & Chein, J. M. (2011). Does working memory training work? The promise and challenges of enhancing cognition by training working memory. *Psychonomic Bulletin & Review*, 18(1), 46–60.

Mullally, S. L., Hassabis, D., & Maguire, E. A. (2012). Scene construction in amnesia: an FMRI study. *The Journal of Neuroscience*, 32(16), 5646–5653.

Murray, E. A., Baxter, M. G., & Gaffan, D. (1998). Monkeys with rhinal cortex damage or neurotoxic hippocampal lesions are impaired on spatial scene learning and object reversals. *Behavioral Neuroscience*, 112(6), 1291–1303.

Murray, E. A., & Bussey, T. J. (1999). Perceptual-mnemonic functions of the perirhinal cortex. *Trends in Cognitive Sciences*, 3(4), 142–151.

Murray, E. A., Bussey, T. J., & Saksida, L. M. (2007). Visual perception and memory: a new view of medial temporal lobe function in primates and rodents. *Annual review of neuroscience*, 30, 99–122.

Murray, E. A., Davidson, M., Gaffan, D., Olton, D. S., & Suomi, S. (1989). Effects of fornix transection and cingulate cortical ablation on spatial memory in rhesus monkeys. *Experimental Brain Research*, 74(1), 173–86.

Murray, E. A., Gaffan, D., & Mishkin, M. (1993). Neural Substrates of Visual Stimulus-Stimulus Association in Rhesus Monkeys. *The Journal of Neuroscience*, 13(10), 4549–4561.

Murray, E. A., & Mishkin, M. (1998). Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. *The Journal of Neuroscience*, 18(16), 6568–6582.

Naggara, O., Oppenheim, C., Rieu, D., Raoux, N., Rodrigo, S., Dalla Barba, G., & Meder, J.-F. (2006). Diffusion tensor imaging in early Alzheimer's disease. *Psychiatry Research*, 146(3), 243–249.

Nairne, J. S. (2002). Remembering over the short term: The case against the standard model. *Annual Review of Psychology*, 53(1), 53–81.

Nestor, P. G., Kubicki, M., Gurrera, R. J., Niznikiewicz, M., Frumin, M., McCarley, R. W., & Shenton, M. E. (2004). Neuropsychological Correlates of Diffusion Tensor Imaging in Schizophrenia. *Neuropsychology*, 18(4), 629–637.

Nestor, P. G., Kubicki, M., Kuroki, N., Gurrera, R. J., Niznikiewicz, M., Shenton, M. E., & McCarley, R. W. (2007). Episodic memory and neuroimaging of hippocampus and fornix in chronic schizophrenia. *Psychiatry Research*, 155(1), 21–28.

Nestor, P. G., Kubicki, M., Niznikiewicz, M., Gurrera, R. J., McCarley, R. W., & Shenton, M. E. (2008). Neuropsychological disturbance in schizophrenia: a diffusion tensor imaging study. *Neuropsychology*, 22(2), 246–254.

Nguyen, D., Vargas, M. I., Khaw, N., Seeck, M., Delavelle, J., Lovblad, K. O., & Haller, S. (2011). Diffusion tensor imaging analysis with tract-based spatial statistics of the white matter abnormalities after epilepsy surgery. *Epilepsy Research*, 94(3), 189–197.

Nichols, E. A., Kao, Y.-C., Verfaellie, M., & Gabrieli, J. D. E. (2006). Working memory and long-term memory for faces: Evidence from fMRI and global amnesia for involvement of the medial temporal lobes. *Hippocampus*, 16(7), 604–616.

Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Human Brain Mapping*, 15(1), 1–25.

Niogi, S. N., Mukherjee, P., Ghajar, J., Johnson, C. E., Kolster, R., Lee, H., Suh, M., et al. (2008). Structural dissociation of attentional control and memory in adults with and without mild traumatic brain injury. *Brain*, 131(12), 3209–3221.

Nitta, M., & Symon, L. (1985). Colloid Cysts of the Third Ventricle A Review of 36 Cases. *Acta neurochirurgica*, 76, 99–104.

Nyberg, L., McIntosh, A. R., Cabeza, R., Nilsson, L. G., Houle, S., Habib, R., & Tulving, E. (1996). Network analysis of positron emission tomography regional cerebral blood flow data: ensemble inhibition during episodic memory retrieval. *The Journal of Neuroscience*, 16(11), 3753–3759.

Olesen, P. J., Westerberg, H., & Klingberg, T. (2004). Increased prefrontal and parietal activity after training of working memory. *Nature Neuroscience*, 7(1), 75–79.

Olman, C. A., Davachi, L., & Inati, S. (2009). Distortion and signal loss in medial temporal lobe. *PLOS ONE*, 4(12), 1–10.

Olson, I. R., Moore, K. S., Stark, M., & Chatterjee, A. (2006). Visual working memory is impaired when the medial temporal lobe is damaged. *Journal of Cognitive Neuroscience*, 18(7), 1087–1097.

Olson, I. R., Page, K., Moore, K. S., Chatterjee, A., & Verfaellie, M. (2006). Working memory for conjunctions relies on the medial temporal lobe. *The Journal of Neuroscience*, 26(17), 4596–4601.

Otten, L. J., Henson, R. N., & Rugg, M. D. (2001). Depth of processing effects on neural correlates of memory encoding: relationship between findings from across- and within-task comparisons. *Brain*, 124(2), 399–412.

Owen, A. M., Hampshire, A., Grahn, J. A., Stenton, R., Dajani, S., Burns, A. S., Howard, R. J., et al. (2010). Putting brain training to the test. *Nature*, 465(7299), 775–778.

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. T. (2005). N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Human Brain Mapping*, 25(1), 46–59.

Owen, A. M., Sahakian, J. S., Polkey, C. E., & Robbins, T. W. (1995). Visuo-spatial short-term recognition memory and learning after temporal lobe excisions, frontal lobe excisions or amygdalo-hippocampectomy in man. *Science*, 33(1), 1–24.

O'Dwyer, L., Lamberton, F., Bokde, A. L. W., Ewers, M., Faluyi, Y. O., Tanner, C., Mazoyer, B., et al. (2011). Multiple indices of diffusion identifies white matter damage in mild cognitive impairment and Alzheimer's disease. *PLOS ONE*, 6(6), 1–13.

O'Keefe, J. (1976). Units in the Hippocampus Moving Rat. *Experimental Neurology*, 51, 78–109.

O'Keefe, J., Burggren, A. C., Donnett, J. G., Jeffery, K. J., & Maguire, E. A. (1998). Place cells, navigational accuracy, and the human hippocampus. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 353(1373), 1333–1340.

O'Keefe, J., & Dostrovsky, J. (1971). The hippocampus as a spatial map: Preliminary evidence from unit activity in the freely-moving rat. *Brain Research*, 34, 171–175.

O'Keefe, J., & Nadel, L. (1978). *The hippocampus as a cognitive map*. Oxford, UK: Clarendon Press.

O'Neil, E. B., Cate, A. D., & Köhler, S. (2009). Perirhinal cortex contributes to accuracy in recognition memory and perceptual discriminations. *The Journal of Neuroscience*, 29(26), 8329–8334.

Papez, J. W. (1937). A Proposed Mechanism of Emotion. *Archives of Neurology and Psychiatry*, 38(4), 725–743.

Perry, R. J., & Hodges, J. R. (1999). Attention and executive deficits in Alzheimer ' s disease: A critical review. *Brain*, 122, 383–404.

Peters, A. (2002). The effects of normal aging on myelin and nerve fibers: A review. *Journal of Neurocytology*, 31(8), 581–593.

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine*, 256(3), 183–194.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild Cognitive Impairment: Clinical Characterization and Outcome. *Archives of Neurology*, 56, 303–308.

Peterson, L. R. (1966). Short-term verbal memory and learning. *Psychological Review*, 73(3), 193–207.

Petrides, M., Alivisatos, B., Meyer, E., & Evans, A. C. (1993). Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proceedings of the National Academy of Sciences of the United States of America*, 90(3), 878–882.

Petrides, M., & Pandya, D. N. (1988). Temporal Region in the Rhesus Monkey. *The Journal of Comparative Neurology*, 273, 52–66.

Piekema, C., Kessels, R. P. C., Mars, R. B., Petersson, K. M., & Fernández, G. (2006). The right hippocampus participates in short-term memory maintenance of object-location associations. *NeuroImage*, 33(1), 374–382.

Poreh, A., Winocur, G., Moscovitch, M., Backon, M., Goshen, E., Ram, Z., & Feldman, Z. (2006). Anterograde and retrograde amnesia in a person with bilateral fornix lesions following removal of a colloid cyst. *Neuropsychologia*, 44(12), 2241–2248.

Postle, B. R., Berger, J. S., & D'Esposito, M. (1999). Functional neuroanatomical double dissociation of mnemonic and executive control processes contributing to working

memory performance. *Proceedings of the National Academy of Sciences of the United States of America*, 96(22), 12959–12964.

Quamme, J. R., Yonelinas, A. P., & Norman, K. A. (2007). Effect of Unitization on Associative Recognition in Amnesia. *Hippocampus*, 17, 192–200.

Raichle, M. E., & Mintun, M. A. (2006). Brain work and brain imaging. *Annual Review of Neuroscience*, 29, 449–476.

Rajah, M. N., & McIntosh, a R. (2006). Dissociating prefrontal contributions during a recency memory task. *Neuropsychologia*, 44(3), 350–364.

Rajaram, S. (1993). Remembering and knowing: two means of access to the personal past. *Memory & Cognition*, 21(1), 89–102.

Ranganath, C. (2010). A unified framework for the functional organization of the medial temporal lobes and the phenomenology of episodic memory. *Hippocampus*, 20(11), 1263–1290.

Ranganath, C., & Blumenfeld, R. S. (2005). Doubts about double dissociations between short- and long-term memory. *Trends in Cognitive Sciences*, 9(8), 374–380.

Ranganath, C., Cohen, M. X., & Brozinsky, C. J. (2005). Working Memory Maintenance Contributes to Long-term Memory Formation: Neural and Behavioral Evidence, 17(7), 994–1010.

Ranganath, C., & Esposito, M. D. (2001). Medial temporal lobe activity association with active maintenance of novel information., 31, 865–873.

Ranganath, C., Flegal, K. E., & Kelly, L. L. (2011). Can Cognitive Training Improve Episodic Memory? *Neuron*, 72(5), 688–691.

Ranganath, C., Yonelinas, A. P., Cohen, M. X., Dy, C. J., Tom, S. M., D'Esposito, M., & D'Esposito, M. (2004). Dissociable correlates of recollection and familiarity within the medial temporal lobes. *Neuropsychologia*, 42(1), 2–13.

Ratcliff, R., Sheu, C. F., & Gronlund, S. D. (1992). Testing global memory models using ROC curves. *Psychological Review*, 99(3), 518–535.

Raven, J. C. (1990). *Advanced Progressive Matrices: Sets I, II*. Oxford, UK: Oxford University Press.

Rebok, G. W., Carlson, M. C., & Langbaum, J. B. S. (2007). Training and Maintaining Memory Abilities in Healthy Older Adults: Traditional and Novel Approaches. *The Journals of Gerontology Series B*, 62(1), 53–61.

Redcay, E., Kleiner, M., & Saxe, R. (2012). Look at this: the neural correlates of initiating and responding to bids for joint attention. *Frontiers in Human Neuroscience*, 6(169), 1–14.

Reed, J. M., & Squire, L. R. (1997). Impaired recognition memory in patients with lesions limited to the hippocampal formation. *Behavioral Neuroscience*, 111(4), 667–675.

Rempel-Clower, N. L., Zola, S. M., Squire, L. R., & Amaral, D. G. (1996). Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. *The Journal of Neuroscience*, 16(16), 5233–5255.

Ringman, J. M., O'Neill, J., Geschwind, D., Medina, L., Apostolova, L. G., Rodriguez, Y., Schaffer, B., et al. (2007). Diffusion tensor imaging in preclinical and presymptomatic carriers of familial Alzheimer's disease mutations. *Brain*, 130(7), 1767–1776.

Rissman, J., Gazzaley, A., & D'Esposito, M. (2008). Dynamic adjustments in prefrontal, hippocampal, and inferior temporal interactions with increasing visual working memory load. *Cerebral Cortex*, 18(7), 1618–1629.

Rosazza, C., & Minati, L. (2011). Resting-state brain networks: literature review and clinical applications. *Neurological Sciences*, 32(5), 773–785.

Rosenbaum, R. S., Winocur, G., Grady, C. L., Ziegler, M., & Moscovitch, M. (2007). Memory for Familiar Environments Learned in the Remote Past : fMRI Studies of Healthy People and an Amnesic Person With Extensive Bilateral Hippocampal Lesions. *Hippocampus*, 1251, 1241–1251.

Ross, R. S., & Slotnick, S. D. (2008). The hippocampus is preferentially associated with memory for spatial context. *Journal of Cognitive Neuroscience*, 20(3), 432–446.

Rotello, C. M., Macmillan, N. A., Reeder, J. A., & Wong, M. (2005). The remember response: subject to bias, graded, and not a process-pure indicator of recollection. *Psychonomic Bulletin & Review*, 12(5), 865–873.

Rotello, C. M., & Zeng, M. (2008). Analysis of RT distributions in the remember—know paradigm. *Psychonomic Bulletin & Review*, 15(4), 825–832.

Rushworth, M. F. S., Ellison, A., & Walsh, V. (2001). Complementary localization and lateralization of orienting and motor attention. *Nature Neuroscience*, 4(6), 656–661.

Saksida, L. M., & Bussey, T. J. (2010). The representational-hierarchical view of amnesia: translation from animal to human. *Neuropsychologia*, 48(8), 2370–2384.

Salat, D. H., Tuch, D. S., van der Kouwe, A. J. W., Greve, D. N., Pappu, V., Lee, S. Y., Hevelone, N. D., et al. (2010). White matter pathology isolates the hippocampal formation in Alzheimer's disease. *Neurobiology of Aging*, 31(2), 244–256.

Salthouse, T. A. (2006). Mental Exercise and Mental Aging. Evaluating the Validity of the "Use It or Lose It" Hypothesis. *Perspectives on Psychological Science*, 1(1), 68–87.

Sasson, E., Doniger, G. M., Pasternak, O., & Assaf, Y. (2010). Structural correlates of memory performance with diffusion tensor imaging. *NeuroImage*, 50(3), 1231–1242.

Saunders, R. C., Mishkin, M., & Aggleton, J. P. (2005). Projections from the entorhinal cortex, perirhinal cortex, presubiculum, and parasubiculum to the medial thalamus in macaque monkeys: identifying different pathways using disconnection techniques. *Experimental Brain Research*, 167(1), 1–16.

Sauvage, M. M., Beer, Z., Ekovich, M., Ho, L., & Eichenbaum, H. (2010). The caudal medial entorhinal cortex: a selective role in recollection-based recognition memory. *The Journal of Neuroscience*, 30(46), 15695–15699.

Sauvage, M. M., Fortin, N. J., Owens, C. B., Yonelinas, A. P., & Eichenbaum, H. (2008). Recognition memory: Opposite effects of hippocampal damage on recollection and familiarity. *Nature Neuroscience*, 11(1), 16–18.

Schacter, D. L., Chui, P., & Ochsner, K. N. (1993). Implicit Memory: A Selective Review. *Annual review of neuroscience*, 16, 159–182.

Schmiedek, F., Lövdén, M., & Lindenberger, U. (2010). Hundred Days of Cognitive Training Enhance Broad Cognitive Abilities in Adulthood: Findings from the COGITO Study. *Frontiers in Aging Neuroscience*, 2, 1–10.

Schneiders, J. A., Opitz, B., Krick, C. M., & Mecklinger, A. (2011). Separating Intra-Modal and Across-Modal Training Effects in Visual Working Memory: An fMRI Investigation. *Cerebral Cortex*, 1–10.

Scholz, J. P., Klein, M. C., Behrens, T. E. J., & Johansen-Berg, H. (2009). Training induces changes in white-matter architecture. *Nature Neuroscience*, 12(11), 1370–1371.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry*, 20(11), 11–21.

Shallice, T., & Warrington, E. K. (1970). Independent functioning of verbal memory stores : A neuropsychological study. *The Quarterly Journal of Experimental Psychology*, 22(2), 261–273.

Shiffrin, R. M., & Atkinson, R. C. (1969). Storage and Retrieval Processes in Long-term Memory. *Psychological Review*, 76(2), 179–193.

Shrager, Y., Gold, J. J., Hopkins, R. O., & Squire, L. R. (2006). Intact visual perception in memory-impaired patients with medial temporal lobe lesions. *The Journal of Neuroscience*, 26(8), 2235–2240.

Shrager, Y., Kirwan, C. B., & Squire, L. R. (2008). Activity in both hippocampus and perirhinal cortex predicts the memory strength of subsequently remembered information. *Neuron*, 59(4), 547–553.

Shulman, G. L., Fiez, J. A., Corbetta, M., Buckner, R. L., Miezin, F. M., Raichle, M. E., & Petersen, S. E. (1997). Common Blood Flow Changes across Visual Tasks : II. Decreases in Cerebral Cortex. *Journal of Cognitive Neuroscience*, 9(5), 648–663.

Sidaros, A., Engberg, A. W., Sidaros, K., Liptrot, M. G., Herning, M., Petersen, P., Paulson, O. B., et al. (2008). Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: a longitudinal study. *Brain*, 131(2), 559–572.

Simons, J. S., Graham, K. S., Galton, C. J., Patterson, K., & Hodges, J. R. (2001). Semantic knowledge and episodic memory for faces in semantic dementia. *Neuropsychology*, 15(1), 101–114.

Smith, E. E., & Jonides, J. (1996). Working memory in humans: neuropsychological evidence. In M. S. Gazzaniga (Ed.), *The Cognitive Neurosciences* (pp. 1009–1020). Cambridge, MA: MIT Press.

Smith, E. E., & Jonides, J. (1997). Working memory: a view from neuroimaging. *Cognitive Psychology*, 33(1), 5–42.

Smith, E. E., & Jonides, J. (1999). Storage and executive processes in the frontal lobes. *Science*, 283(5408), 1657–1661.

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, 17(3), 143–155.

Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., Filippini, N., et al. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America*, 106(31), 13040–13045.

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., Watkins, K. E., et al. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *NeuroImage*, 31(4), 1487–1505.

Song, M., Zhou, Y., Li, J., Liu, Y., Tian, L., Yu, C., & Jiang, T. (2008). Brain spontaneous functional connectivity and intelligence. *NeuroImage*, 41(3), 1168–1176.

Spencer, S. S. (2002). Neural networks in human epilepsy: evidence of and implications for treatment. *Epilepsia*, 43(3), 219–27.

Spiers, H. J., Burggren, A. C., Maguire, E. A., Baxendale, S. A., Hartley, T., Thompson, P. J., & O'Keefe, J. (2001). Unilateral temporal lobectomy patients show lateralized topographical and episodic memory deficits in a virtual town. *Brain*, 124(12), 2476–2489.

Squire, L. R. (1980). The anatomy of amnesia. *Trends in Neurosciences*, 3(3), 52–54.

Squire, L. R. (1986). Mechanisms of memory. *Science*, 232(4758), 1612–1619.

Squire, L. R. (2009). The legacy of patient H.M. for neuroscience. *Neuron*, 61(1), 6–9.

Squire, L. R., Amaral, D. G., & Press, G. A. (1990). Magnetic resonance imaging of the hippocampal formation and mammillary nuclei distinguish medial temporal lobe and diencephalic amnesia. *The Journal of Neuroscience*, 10(9), 3106–3117.

Squire, L. R., Knowlton, B. J., & Musen, G. (1993). The structure and organisation of memory. *Annual Review of Psychology*, 44, 453–495.

Squire, L. R., & Slater, P. C. (1978). Anterograde and retrograde memory impairment in chronic amnesia. *Neuropsychologia*, 16(3), 313–322.

Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). The medial temporal lobe. *Annual review of neuroscience*, 27, 279–306.

Squire, L. R., Wixted, J. T., & Clark, R. E. (2007). Recognition memory and the medial temporal lobe: a new perspective. *Nature Reviews Neuroscience*, 8(11), 872–883.

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science*, 253(5026), 1380–1386.

Staresina, B. P., & Davachi, L. (2006). Differential encoding mechanisms for subsequent associative recognition and free recall. *The Journal of Neuroscience*, 26(36), 9162–9172.

Staresina, B. P., & Davachi, L. (2008). Selective and shared contributions of the hippocampus and perirhinal cortex to episodic item and associative encoding. *Journal of Cognitive Neuroscience*, 20(8), 1478–1489.

Staresina, B. P., Duncan, K. D., & Davachi, L. (2011). Perirhinal and parahippocampal cortices differentially contribute to later recollection of object- and scene-related event details. *The Journal of Neuroscience*, 31(24), 8739–8747.

Stebbins, G. T., & Murphy, C. M. (2010). Diffusion tensor imaging in Alzheimer's disease and mild cognitive impairment. *Behavioural Neurology*, 21(1), 39–49.

Stefanacci, L., Buffalo, E. A., Schmolck, H., & Squire, L. R. (2000). Profound amnesia after damage to the medial temporal lobe: A neuroanatomical and neuropsychological profile of patient E. P. *The Journal of Neuroscience*, 20(18), 7024–7036.

Stern, C. E., Sherman, S. J., Kirchhoff, B. A., & Hasselmo, M. E. (2001). Medial temporal and prefrontal contributions to working memory tasks with novel and familiar stimuli. *Hippocampus*, 11(4), 337–346.

Supekar, K., Menon, V., Rubin, D., Musen, M., & Greicius, M. D. (2008). Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. *PLOS Computational Biology*, 4(6), 1–11.

Suzuki, W. A. (2009). Perception and the medial temporal lobe: evaluating the current evidence. *Neuron*, 61(5), 657–66.

Sweet, W. H., Talland, G. A., & Ervin, F. R. (1959). Loss of recent memory following section of fornix. *Transactions of the American Neurological Association*, (84), 76–82.

Takahashi, M., Iwamoto, K., Fukatsu, H., Naganawa, S., Iidaka, T., & Ozaki, N. (2010). White matter microstructure of the cingulum and cerebellar peduncle is related to sustained attention and working memory: a diffusion tensor imaging study. *Neuroscience letters*, 477(2), 72–76.

Takahashi, S., Yonezawa, H., Takahashi, J., Kudo, M., Inoue, T., & Tohgi, H. (2002). Selective reduction of diffusion anisotropy in white matter of Alzheimer disease brains measured by 3.0 Tesla magnetic resonance imaging. *Neuroscience letters*, 332(1), 45–48.

Takeuchi, H., Sekiguchi, A., Taki, Y., Yokoyama, S., Yomogida, Y., Komuro, N., Yamanouchi, T., et al. (2010). Training of Working Memory Impacts Structural Connectivity. *The Journal of Neuroscience*, 30(9), 3297–3303.

Tambini, A., Ketz, N., & Davachi, L. (2010). Enhanced Brain Correlations during Rest Are Related to Memory for Recent Experiences. *Neuron*, 65(2), 280–290.

Taylor, K. J., Henson, R. N., & Graham, K. S. (2007). Recognition memory for faces and scenes in amnesia: dissociable roles of medial temporal lobe structures. *Neuropsychologia*, 45(11), 2428–2438.

Thorell, L. B., Lindqvist, S., Bergman Nutley, S., Bohlin, G., & Klingberg, T. (2009). Training and transfer effects of executive functions in preschool children. *Developmental Science*, 12(1), 106–113.

Toepper, M., Markowitsch, H. J., Gebhardt, H., Beblo, T., Thomas, C., Gallhofer, B., Driessen, M., et al. (2010). Hippocampal involvement in working memory encoding of changing locations: an fMRI study. *Brain research*, 1354, 91–99.

Trachtenberg, A. J., Filippini, N., Ebmeier, K. P., Smith, S. M., Karpe, F., & Mackay, C. E. (2011). The effects of APOE on the functional architecture of the resting brain. *NeuroImage*, 59, 565–572.

Tsivilis, D., Vann, S. D., Denby, C. E., Roberts, N., Mayes, A. R., Montaldi, D., & Aggleton, J. P. (2008). A disproportionate role for the fornix and mammillary bodies in recall versus recognition memory. *Nature Neuroscience*, 11(7), 834–842.

Tulving, E. (1983). *Elements of episodic memory*. New York, NY: Oxford University Press.

Tulving, E. (1985). Memory and Consciousness. *Canadian Psychologist*, 26, 1–12.

Tulving, E. (2002). Episodic Memory : From Mind to Brain. *Annual Review of Psychology*, 53, 1–25.

Tulving, E., & Donaldson, W. (1972). Episodic and Semantic Memory. *Organization of memory*. New York, NY: Academic Press.

Ungerleider, L. G., Gaffan, D., & Pelak, V. S. (1989). Projections from inferior temporal cortex to prefrontal cortex via the uncinate fascicle in rhesus monkeys. *Experimental Brain Research*, 76, 473–484.

Ungerleider, L. G., & Mishkin, M. (1982). Two cortical visual systems. In D. Ingle, M. Goodal, & R. Mansfield (Eds.), *Analysis of Visual Behavior* (pp. 549–586). Boston, MA: MIT Press.

Vann, S. D., Tsivilis, D., Denby, C. E., Quamme, J. R., Yonelinas, A. P., Aggleton, J. P., Montaldi, D., et al. (2009). Impaired recollection but spared familiarity in patients with extended hippocampal system damage revealed by 3 convergent methods. *Proceedings of the National Academy of Sciences of the United States of America*, 106(13), 5442–5447.

Vargha-Khadem, F. (1997). Differential Effects of Early Hippocampal Pathology on Episodic and Semantic Memory. *Science*, 277(5324), 376–380.

Vincent, J. L., Patel, G. H., Fox, M. D., Snyder, A. Z., Baker, J. T., Van Essen, D. C., Zempel, J. M., et al. (2007). Intrinsic functional architecture in the anaesthetized monkey brain. *Nature*, 447(7140), 83–86.

Voets, N. L., Adcock, J. E., Stacey, R., Hart, Y., Carpenter, K., Matthews, P. M., & Beckmann, C. F. (2009). Functional and structural changes in the memory network associated with left temporal lobe epilepsy. *Human Brain Mapping*, 30(12), 4070–4081.

Voets, N. L., Beckmann, C. F., Cole, D. M., Hong, S., Bernasconi, A., & Bernasconi, N. (2012). Structural substrates for resting network disruption in temporal lobe epilepsy. *Brain*, 135(8), 2350–2357.

Wagner, A. D., Schacter, D. L., Rotte, M., Koutstaal, W., Maril, A., Dale, A. M., Rosen, B. R., et al. (1998). Building Memories: Remembering and Forgetting of Verbal Experiences as Predicted by Brain Activity. *Science*, 281(5380), 1188–1191.

Wais, P. E., Mickes, L., & Wixted, J. T. (2008). Remember/know judgments probe degrees of recollection. *Journal of Cognitive Neuroscience*, 20(3), 400–405.

Wais, P. E., Wixted, J. T., Hopkins, R. O., & Squire, L. R. (2006). The hippocampus supports both the recollection and the familiarity components of recognition memory. *Neuron*, 49(3), 459–466.

Walker, J. A., & Olton, D. S. (1979). Spatial memory deficit following fimbria-fornix lesions: independent of time for stimulus processing. *Physiology & Behavior*, 23(1), 11–15.

Waller, A. (1850). Experiments on the section of the glossopharyngeal and hypoglossal nerves of the frog, and observations of the alterations produced thereby in the structure of their primitive fibres. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 140, 423–429.

Wang, L., Zang, Y.-F., He, Y., Liang, M., Zhang, X., Tian, L., Wu, T., et al. (2006). Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence from resting state fMRI. *NeuroImage*, 31(2), 496–504.

Warrington, E. K. (1984). *Recognition Memory Test.* Windsor, UK: NFER-Nelson.

Warrington, E. K., & Shallice, T. (1969). The selective impairment of auditory verbal short-term memory. *Brain*, 92(4), 885–896.

Watson, H. C., Wilding, E. L., & Graham, K. S. (2012). A role for perirhinal cortex in memory for novel object-context associations. *The Journal of Neuroscience*, 32(13), 4473–4481.

Waugh, N. C., & Norman, D. (1965). Primary Memory. *Psychological Review*, 72(2), 89–104.

Wechsler, D. (1999). *The Wechsler Memory Scale - Third Edition*. San Antonio (TX): Psychological Corporation.

Weiskrantz, L. (1971). Comparison of amnesic states in monkey and man. *Cognitive processes of nonhuman primates*. New York, NY: Academic Press.

Welsh, K. A., Butters, N., Hughes, J., Mohs, R. C., & Heyman, A. (1992). Detection and Staging of Dementia in Alzheimer ' s Disease. *Archives of Neurology*, 49, 448–452.

Westerberg, H., Jacobaeus, H., Hirvikoski, T., Clevberger, P., Östensson, M.-L., Bartfai, A., & Klingberg, T. (2007). Computerized working memory training after stroke–A pilot study. *Brain Injury*, 21(1), 21–29.

Whitwell, J. L., Przybelski, S. a, Weigand, S. D., Knopman, D. S., Boeve, B. F., Petersen, R. C., & Jack, C. R. (2007). 3D maps from multiple MRI illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to Alzheimer's disease. *Brain*, 130(7), 1777–1786.

Williams, P., & Simons, D. J. (2000). Detecting Changes in Novel , Complex Three- dimensional Objects. *Visual Cognition*, 7(1-3), 297–322.

Willis, S. L., Tennstedt, S. L., Marsiske, M., Ball, K., Elias, J., Koepke, K. M., Morris, J. N., et al. (2006). Long-term effects of cognitive training on everyday functional outcomes in older adults. *The Journal of the American Medical Association*, 296(23), 2805–2814.

Wilson, B. A. (2008). Neuropsychological rehabilitation. *Annual Review of Clinical Psychology*, 4, 141–162.

Wixted, J. T. (2007). Dual-process theory and signal-detection theory of recognition memory. *Psychological Review*, 114(1), 152–176.

Wixted, J. T., & Squire, L. R. (2004). Recall and recognition are equally impaired in patients with selective hippocampal damage. *Cognitive, Affective, & Behavioral Neuroscience*, 4(1), 58–66.

Woodard, J. L., Seidenberg, M., Nielson, K. a, Antuono, P., Guidotti, L., Durgerian, S., Zhang, Q., et al. (2009). Semantic memory activation in amnestic mild cognitive impairment. *Brain*, 132(8), 2068–2078.

Xiong, J., Parsons, L. M., Gao, J., & Fox, P. T. (1999). Interregional Connectivity to Primary Motor Cortex Revealed Using MRI Resting State Images. *Human Brain Mapping*, 156, 151–156.

Yonelinas, A. P. (1994). Receiver-operating characteristics in recognition memory: evidence for a dual-process model. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 20(6), 1341–1354.

Yonelinas, A. P. (2001). Components of episodic memory: the contribution of recollection and familiarity. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 356(1413), 1363–1374.

Yonelinas, A. P. (2002). The Nature of Recollection and Familiarity: A Review of 30 Years of Research. *Journal of Memory and Language*, 46(3), 441–517.

Yonelinas, A. P., & Jacoby, L. L. (1995). The relation between remembering and knowing as bases for recognition: Effects of size congruency. *Journal of Memory and Language*, 34, 622–643.

Yonelinas, A. P., Kroll, N. E., Dobbins, I. G., Lazzara, M. M., & Knight, R. T. (1998). Recollection and familiarity deficits in amnesia: convergence of remember-know, process dissociation, and receiver operating characteristic data. *Neuropsychology*, 12(3), 323–339.

Yonelinas, A. P., Kroll, N. E., Quamme, J. R., Lazzara, M. M., Sauve, M. J., Widaman, K. F., & Knight, R. T. (2002). Effects of extensive temporal lobe damage or mild hypoxia on recollection and familiarity. *Nature Neuroscience*, 5(11), 1236–1241.

Yonelinas, A. P., Otten, L. J., Shaw, K. N., & Rugg, M. D. (2005). Separating the Brain Regions Involved in Recollection and Familiarity in Recognition Memory. *The Journal of Neuroscience*, 25(11), 3002–3008.

Yonelinas, A. P., & Parks, C. M. (2007). Receiver operating characteristics (ROCs) in recognition memory: a review. *Psychological Bulletin*, 133(5), 800–832.

Yoo, S.-S., Paralkar, G., & Panych, L. P. (2004). Neural substrates associated with the concurrent performance of dual working memory tasks. *The International Journal of Neuroscience*, 114(6), 613–631.

Zhang, H. Y., Wang, S., Liu, B., Ma, Z. L., Yang, M., Zhang, Z. J., & Teng, G. J. (2010). Resting Brain Connectivity : Changes during the Progress of Alzheimer Disease. *Radiology*, 256(2), 598–606.

Zhang, Y., Brady, M., & Smith, S. M. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Transactions on Medical Imaging*, 20(1), 45–57.

Zhang, Z., Lu, G., Zhong, Y., Tan, Q., Liao, W., Chen, Z., Shi, J., et al. (2009). Impaired perceptual networks in temporal lobe epilepsy revealed by resting fMRI. *Journal of Neurology*, 256(10), 1705–1713.

Zhang, Z., Lu, G., Zhong, Y., Tan, Q., Liao, W., Wang, Z., Wang, Z., et al. (2010). Altered spontaneous neuronal activity of the default-mode network in mesial temporal lobe epilepsy. *Brain research*, 1323, 152–160.

Zhang, Z., Lu, G., Zhong, Y., Tan, Q., Yang, Z., Liao, W., Chen, Z., et al. (2009). Impaired attention network in temporal lobe epilepsy: a resting FMRI study. *Neuroscience letters*, 458(3), 97–101.

Zhou, J., Greicius, M. D., Gennatas, E. D., Growdon, M. E., Jang, J. Y., Rabinovici, G. D., Kramer, J. H., et al. (2010). Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain*, 133(5), 1352–1367.

Zola-Morgan, S., Squire, L. R., & Amaral, D. G. (1986). Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *The Journal of Neuroscience*, 6(10), 2950–2967.

Zola-Morgan, S., Squire, L. R., Amaral, D. G., & Suzuki, W. A. (1989). Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. *The Journal of Neuroscience*, 9(12), 4355–4370.

Zola-Morgan, S., Squire, L. R., Clower, R. P., & Rempel-Clower, N. L. (1993). Damage to the perirhinal cortex exacerbates memory impairment following lesions to the hippocampal formation. *The Journal of Neuroscience*, 13(1), 251–265.

Zola-Morgan, S., Squire, L. R., & Ramus, S. J. (1994). Severity of memory impairment in monkeys as a function of locus and extent of damage within the medial temporal lobe memory system. *Hippocampus*, 4(4), 483–495.

Zou, Q., Ross, T. J., Gu, H., Geng, X., Zuo, X.-N., Hong, L. E., Gao, J.-H., et al. (2012). Intrinsic resting-state activity predicts working memory brain activation and behavioral performance. *Human Brain Mapping*, (126), 1–12.

Zuo, X.N., Kelly, C., Adelstein, J. S., Klein, D. F., Castellanos, X. F., & Milham, M. P. (2010). Reliable intrinsic connectivity networks: test-retest evaluation using ICA and dual regression approach. *NeuroImage*, 49(3), 2163–2177.